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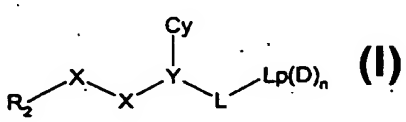


(I)

(57) Abstract: Compounds of formula (I) where R_2, each X, L, Y, Cy, Lp, D and n are as defined in the specification, are serine protease (especially tryptase) inhibitors useful as antiinflammatory agents.

Compounds

This invention relates to compounds which are inhibitors of serine proteases and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body. More particularly it relates to compounds for use in the treatment of mast cell mediated diseases such as asthma and other allergic and inflammatory conditions and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body, and in particular to compounds which are tryptase inhibitors.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood.

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological process including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical

cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Asthma, the most prevalent of all mast cell mediated conditions affects about 5% of the population in industrialised countries and there is evidence that its incidence and severity are on the increase. Furthermore, the incidence of childhood asthma is rising and there are suggestions of a link between environmental pollutants and the onset of the disease.

Initially, it was believed that bronchoconstriction, i.e. the narrowing of the airways in the lungs, was the major feature of asthma. However, it is now recognised that inflammation in the lungs is an integral part of the development of the disease.

The inhalation of an allergen by an asthmatic generates a strong immune system response which triggers release of various inflammatory mediators, including histamine and

leukotrienes from inflammatory cells. These increase the permeability of the blood vessel walls, attract inflammatory cells into the tissues and contract the smooth muscle around the airways. As a result, fluid leaks from the blood and the tissues swell, further narrowing the airways. The inflammatory cells cause damage to the epithelial cells lining the airways exposing nerve endings which stimulates secretion of mucous as well as augmenting the inflammation by causing the release of neurokinins.

Thus asthma is a complex disease frequently characterised by progressive developments of hyper-responsiveness of the trachea and bronchi as a result of chronic inflammation reactions which irritate the epithelium lining the airway and cause pathological thickening of the underlying tissues.

Leukocytes and mast cells are present in the epithelium and smooth muscle tissue of the bronchi where they are activated initially by binding of specific inhaled antigens to IgE receptors. Activated mast cells release a number of preformed or primary chemical mediators of the inflammatory response in asthma as well as enzymes. Moreover, secondary mediators of inflammation are generated by enzymatic reactions of activated mast cells and a number of large molecules are released by degranulation of mast cells.

It has therefore been proposed that chemical release from mast cells probably accounts for the early bronchiolar constriction response that occurs in susceptible individuals after exposure to airborne allergens. The early asthmatic reaction is maximal at around 15 minutes after allergen exposure, recovery occurring over the ensuing 1 to 2 hours.

In approximately 30% of individuals, the early asthmatic reaction is followed by a further decline in respiratory function which normally begins within a few hours and is maximal between 6 and 12 hours after exposure. This late asthmatic reaction is accompanied by a marked increase in the number of inflammatory cells infiltrating bronchiolar smooth muscle and epithelial tissues, and spilling into the airways. These cells are attracted to the site by release of mast cell derived chemotactic agents.

The most straightforward way of dealing with an asthma attack is with a bronchodilator drug which causes airways to expand. The most effective bronchodilators are the β-adrenergic agonists which mimic the actions of adrenalin. These are widely used and are simply administered to the lungs by inhalers. However, bronchoconstrictor drugs are primarily of use in short term symptomatic relief, and do not prevent asthma attacks nor deterioration of lung function over the long term.

Anti-inflammatory drugs such as cromoglycate and the corticosteroids are also widely used in asthma therapy. Cromoglycate has anti-inflammatory activity and has been found to be extremely safe. Although such cromolyns have minimal side effects and are currently preferred for initial preventive therapy in children, it is well known that they are of limited efficacy.

The use of corticosteroids in asthma therapy was a major advance since they are very effective anti-inflammatory agents, however, steroids are very powerful, broad spectrum anti-inflammatory agents and their potency and non-specificity means that they are seriously limited by

adverse side effects. Localising steroid treatment to the lungs using inhaler technology has reduced side effects but the reduced systemic exposure following inhalation still results in some undesirable effects. Hence, there is a reluctance to use steroids early in the course of the disease.

There therefore still remains a need for an alternative asthma therapy which is a safe, effective, anti-inflammatory or immunomodulatory agent which can be taken to treat chronic asthma.

Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation. Tryptase is one of a large number of serine protease enzymes which play a central role in the regulation of a wide variety of physiological processes including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. Although a large number of serine proteases have been widely investigated, tryptase still remains relatively unexplored.

Mature human tryptase is a glycosylated, heparin-associated tetramer of catalytically active subunits. Its amino-acid structure appears to have no close counterpart among the other serine proteases which have been characterised. Tryptase is stored in mast cell secretory granules and after mast cell activation, human tryptase can be measured readily in a variety of biological fluids. For example, after anaphylaxis, tryptase appears in the blood stream where it is readily detectable for several hours. Tryptase also appears in samples of nasal and lung lavage

fluid from atopic subjects challenged with specific antigen. Tryptase has been implicated in a variety of biological processes where activation and degranulation of mast cells occur. Accordingly, mast cell tryptase inhibition may be of great value in the prophylaxis and treatment of a variety of mast cell mediated conditions. Mast cells can degranulate by both IgE-dependent and independent mechanisms thereby implicating tryptase in both atopic and non-atopic inflammatory conditions. Tryptase can activate proteases such as pro-urokinase and pro-MMP3 (pro-matrix metalloprotease 3, pro-stromelysin), thereby indicating a pathological role in tissue inflammation and remodelling. Furthermore, the recent evidence that tryptase can activate certain G-protein coupled receptors (eg PAR2) and induce neurogenic inflammation points to a broader physiological role, for example in modulating pain mechanisms. Given tryptase's multiple mechanisms of action, it has been proposed that tryptase inhibitors may be beneficial in a broad range of diseases. These include conditions such as: asthma (specifically influencing the inflammatory component, the underlying hyperreactivity, and the chronic fibrotic damage due to smooth muscle thickening); chronic obstructive pulmonary disease (COPD) and pulmonary fibrotic diseases; rhinitis; psoriasis; urticaria; dermatitis; arthritis; Crohn's disease; colitis; angiogenesis; atherosclerosis; multiple sclerosis; interstitial cystitis; migraine headache; neurogenic inflammation and pain mechanisms; wound healing; cirrhosis of the liver; Kimura's disease; pre-eclampsia; bleeding problems associated with menstruation and the menopause; cancer (particularly melanoma and tumour

metastasis); pancreatitis; and certain viral infections (Yong, Exp. Toxic Pathol, 1997, 49, 409; Steinhoff et al., Nat. Med., 2000, 6, 151; Downing and Miyan, Immunol. Today, 2000, 21, 281; Tetlow and Wooley, Ann. Rheum. Dis., 1995, 54, 549; Jeziorska, Salamonsen and Wooley, Biol. Reprod., 1995, 53, 312; Brain, Nat. Med., 2000, 6, 134; Olness et al., Headache, 1999, 39, 101.) The underlying principle is that a tryptase inhibitor should have utility where mast cells have being induced to degranulate by whatever mechanism, including anaphylactic reactions due to exogenous substances, e.g. morphine-induced bronchoconstriction (Bowman and Rand, 2nd edt., 1980.)

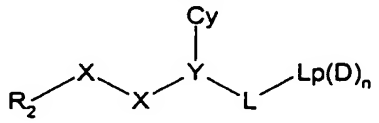
In WO96/09297, WO95/32945, WO94/20527 and US 5,525,623 a variety of peptide based compounds are suggested as potential inhibitors of the mast cell protease tryptase. In WO95/03333 a tryptase inhibitor is provided by a polypeptide obtainable from the leech *Hirudo medicinalis*. In WO96/08275 secretory leukocyte protease inhibitor (SLPI) and active fragments thereof have been found to inhibit the proteolytic activity of tryptase. In WO99/55661 certain 4-aminomethylbenzoic ester derivatives are proposed as potential tryptase inhibitors.

We have now found that certain aromatic compounds carrying lipophilic side chains are particularly effective as inhibitors of the serine protease, tryptase.

It is envisaged that the compounds of the invention will be useful not only in the treatment and prophylaxis of asthma but also of other allergic and inflammatory conditions mediated by tryptase such as allergic rhinitis, skin conditions such as eczema, psoriasis, atopic dermatitis

and urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel disease, neurogenic inflammation, atherosclerosis and cancer.

Thus viewed from one aspect the invention provides a serine protease inhibitor compound of formula (I)



(I)

where R_2 represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, substituted in the 3 and/or 4 position by R_1, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, hydroxyalkyl, alkoxy or alkylthio;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_1 independently represents aminoalkyl;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl

imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group;

D is a hydrogen bond donor group;

n is 0, 1 or 2;

R_{1a} represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl; and

R_{1b} and R_{1c} are as defined for R_{1a};

or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

Compounds of formula I have surprisingly been found to be particularly effective as inhibitors of tryptase and to show a surprising selectivity for tryptase over other serine proteases.

In the compounds of the invention, where the alpha atom is carbon it preferably has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X. Likewise the fourth substituent R_{1b} at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of the invention, unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C_{1-6} or C_{1-3}; cyclic groups preferably have ring sizes of 3 to 8 atoms;

and fused multicyclic groups preferably contain 8 to 16 ring atoms.

R_{1a} is preferably hydrogen.

The linker group from the R_2 group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -$CONR_{1a}$-, -NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH_2 or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-.

Examples of particular values for R_{1b} are: hydrogen or (1-4C)alkyl, such as methyl. R_{1b} is preferably a hydrogen atom.

The alpha atom (Y) is preferably a CH or $C(CH_3)$ group, especially CH.

The linker group from the alpha atom to the lipophilic group is preferably CO, CH_2NH, $CONR_{1d}(CH_2)_m$, $(CH_2)_mN(R_{1d})CO(CH_2)_m$, $(CH_2)_{m+2}$, $CO(CH_2)_m$, $(CH_2)_mCO$, $(CH_2)_mOC=O$, $(CH_2)_mO$, $CH=CH(CH_2)_m$, SO_2, SO_2NR_{1d}, $SO_2(CH_2)_m$, $(CH_2)_mSO_2$ or $(CH_2)_mSO_2NR_{1d}$ (where each m is independently 0 or 1 and R_{1d} is as defined for R_{1a}).

Examples of particular values for R_{1d} are:
hydrogen; and
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as methyl or ethyl, or aryl(1-6C)alkyl, such as benzyl or phenylethyl.

R_{1d} is preferably hydrogen.

The linker may be optionally branched, for example, to incorporate a polar functionality.

Examples of particular values for L are CO, CONH, CH_2NHCO and $CONHCH_2$, more preferably CO or CONH.

It will be appreciated by those skilled in the art that a diverse range of organic groups are lipophilic, and that it is therefore impractical to define with precision each and every structure that may be incorporated into a serine protease inhibitor according to the invention. Accordingly, it is being assumed that the addressee of this specification will not require an exhaustive computer listing of structures of lipophilic groups, but will instead make use of the structures of lipophilic groups disclosed in the specification, especially those exemplified; the test systems described herein for identifying serine protease inhibitors; and common general knowledge of the lipophilicity, synthesis and stability of organic compounds, to obtain novel serine protease inhibitor compounds of formula (I).

The lipophilic group may be, for example, an alkyl, alkenyl, carbocyclic or heterocyclic group, or a combination of two or more such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, NR_{1e}-CO-, NR_{1e} linkage (where R_{1e} is as defined for R_{1a}), optionally substituted by one or more oxo or R_3 groups in which R_3 is alkylaminocarbonyl, alkoxycarbonylamino, N-alkylaminoalkanoyl, N-alkanoylaminoalkanonyl, C-hydroxyaminoalkanoyl or is as defined for R_{3a}.

When the lipophilic group comprises an alkyl group, this may be, for example, a (1-3C) alkyl group, such as methyl, ethyl or propyl. Preferably an alkyl group is unsubstituted.

When the lipophilic group comprises a carbocyclic group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic hydrocarbon group containing up to 25, more preferably up to 10 carbon atoms. The carbocyclic group may thus be, for example, a cycloalkyl, polycycloalkyl, phenyl or naphthyl group, or a cycloalkyl group fused with a phenyl group.

Examples of particular values for a cycloalkyl group are (3-6C) cycloalkyl groups, such as cyclopentyl and cyclohexyl. A cycloalkyl group is preferably unsubstituted or substituted by one group R_3, preferably an amino or alkyl group.

Examples of particular values for a polycycloalkyl group are (6-10C) polycycloalkyl groups, such as bicycloalkyl, for example decalinyl, norbornyl or adamantyl. A polycycloalkyl group is preferably unsubstituted or substituted by one, two or three R_3 groups, for example alkyl such as methyl. An example of a polycycloalkyl group substituted by alkyl is isopinocampheyl.

A phenyl group is preferably unsubstituted or substituted by one or two R_3 groups.

A naphthyl group is preferably unsubstituted or substituted by one R_3 group.

Examples of a cycloalkyl or cycloalkenyl group fused with a phenyl group are indanyl and tetrahydronaphthyl. This group is preferably unsubstituted or substituted by oxo or one or two R_3 groups. Examples of groups substituted by oxo are 1-oxoindan-5-yl, 1-oxo-5,6,7,8-tetrahydronaphth-5-yl and 1-oxo-5,6,7,8-tetrahydro-naphth-6-yl.

When the lipophilic group comprises a heterocyclic

group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic group containing one or two oxygen, nitrogen or sulfur atoms in the ring system, and in total up to 25, more preferably up to 10 ring system atoms.

Examples of a heterocyclic group when it is a non-aromatic monocyclic group are azacycloalkyl groups, such as pyrrolidinyl and piperidinyl; azacycloalkenyl groups, such as pyrrolinyl; diazacycloalkyl groups, such as piperazinyl; oxacycloalkyl groups, such as tetrahydropyranyl; and thiacycloalkyl groups, such as tetrahydrothiopyranyl. A non-aromatic monocyclic group preferably contains 5, 6 or 7 ring atoms and is preferably unsubstituted or substituted by one group R_3.

Examples of a heterocyclic group when it is a non-aromatic polycyclic group are bicyclic groups, such as azacycloalkyl fused with phenyl, for example dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl and tetrahydroisoquinolinyl; and azacycloalkyl fused with cycloalkyl, such as decahydroisoquinolinyl.

Examples of a heterocyclic group when it is a aromatic monocyclic group are furyl, pyrrolyl, thienyl, imidazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, preferably unsubstituted or substituted by one or two R_3 groups.

Examples of a heterocyclic group when it is an aromatic polycyclic group are bicyclic groups such as benzofuryl, quinolinyl, isoquinolinyl, benzothienyl, indolyl and benzothiazolyl.

The lipophilic group preferably comprises a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl,

bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl or alkenyl group all optionally substituted by one or more oxo or groups R_3, or a combination of at least two such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, NR_{1e}-CO- or NR_{1e} linkage (where R_{1e} is as defined for R_{1a}).

Where Lp comprises a combination of at least two groups, it preferably comprises a combination of two or three such groups. The groups are preferably linked by a single bond, C=O, O or NR_{1e}.

Examples of particular values for R_3 are:-

for alkylaminocarbonyl: N-methyl-N-ethylaminocarbonyl;

for N-alkylaminoalkanoyl: N-methylacetyl;

for N-alkanoylaminoalkanonyl: 2-N-acetylaminoacetyl or 2-N-acetylaminopropanoyl;

for C-hydroxyaminoalkanoyl: 2-amino-3-hydroxypropanoyl or 2-amino-3-hydroxybutanoyl;

hydrogen;

hydroxyl;

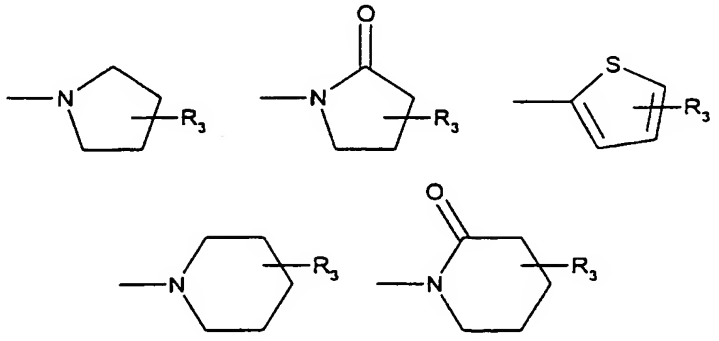
for alkoxy optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkoxy such as methoxy;

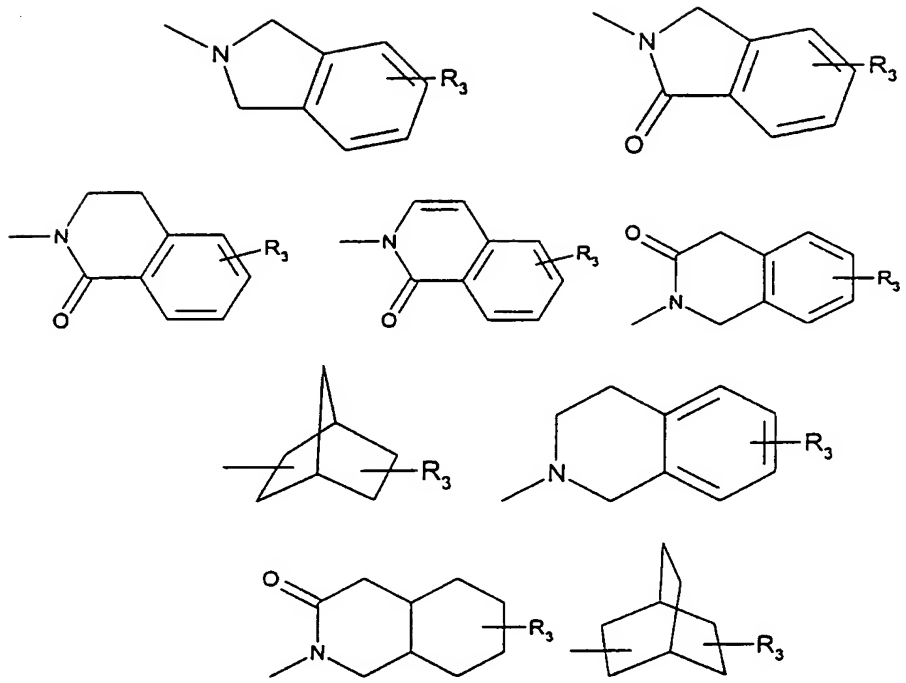
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl, ethyl, propyl, and 2-propyl, or (1-6C)alkanoyl, such as acetyl, propionyl or isobutyryl;

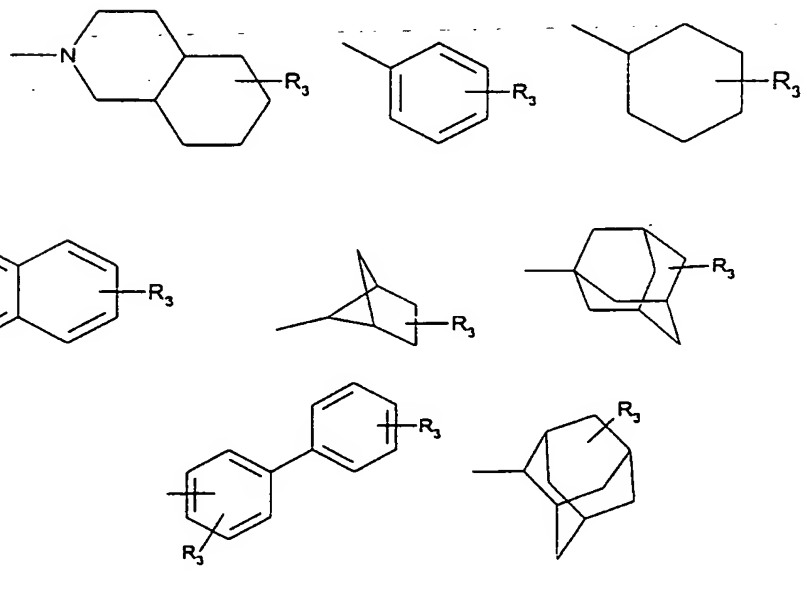
for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amino(1-6C)alkyl, such as aminomethyl, amido ($CONH_2$), and amino(1-6C)alkanoyl, such as aminoacetyl ($COCH_2NH_2$), aminopropionyl

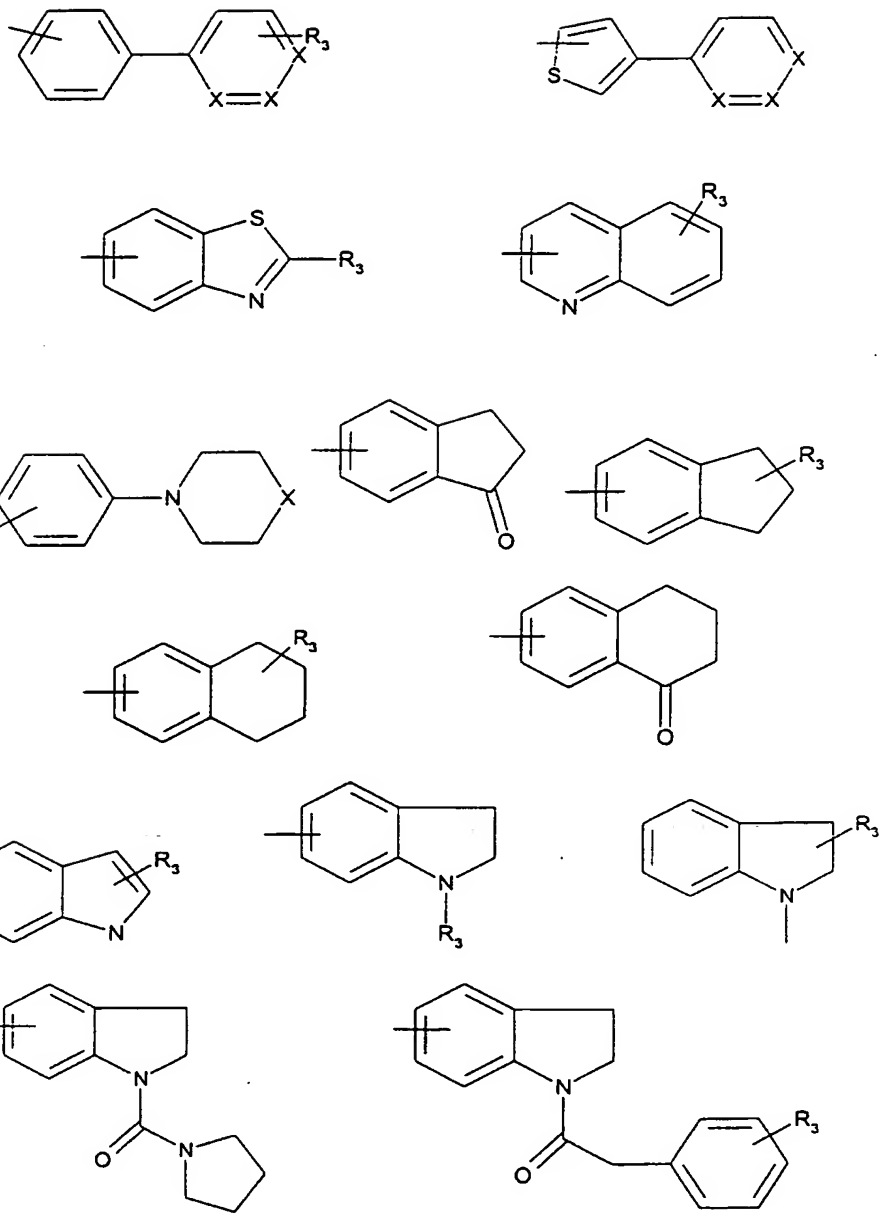
($COCH_2CH_2NH_2$) or 2-aminopropionyl ($COCH(CH_3)NH_2$);
for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxy(1-6C)alkyl, such as hydroxymethyl or 1-hydroxyethyl, or hydroxy(1-6C)alkanoyl, such as 2-hydroxyacetyl or 2-hydroxypropanoyl;
for alkoxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkoxy(1-6C)alkyl such as methoxymethyl;
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as formylamino or acetylamino;
amino;
for halo: chloro;
cyano;
nitro;
thiol;
for alkylthio: methylthio;
for alkylsulphonyl: methylsulphonyl;
for alkylsulphenyl: methylsulphenyl; and
hydrazido.

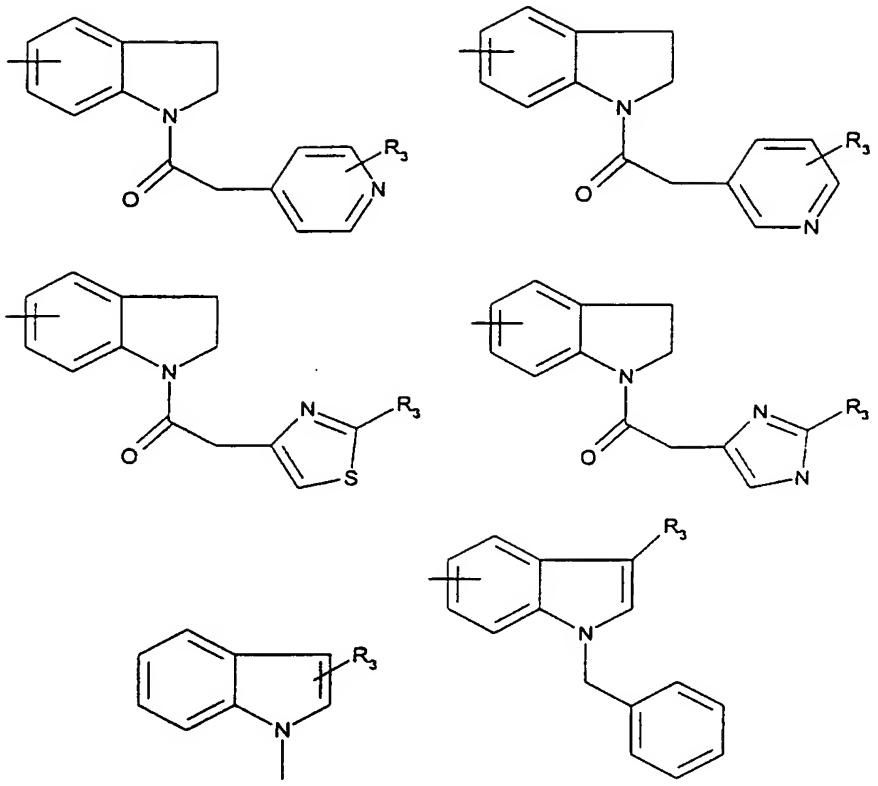
Most preferably, the lipophilic group is selected from









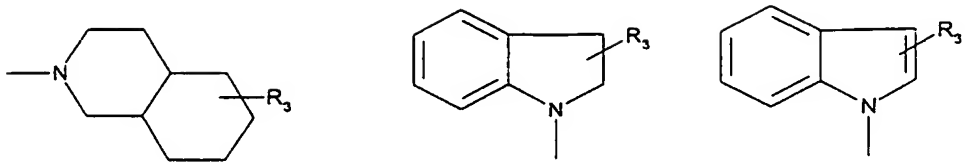


wherein R_3 is as hereinbefore defined; and

X represents CH or N.

In the Lp groups depicted above, preferably L represents CO when the Lp group is linked to L through N, or CONH when the Lp group is linked to L through C.

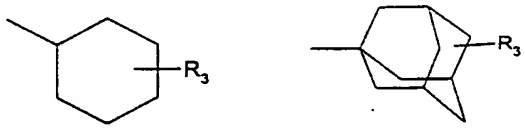
One group of compounds of particular interest is that in which L represents CO and Lp represents

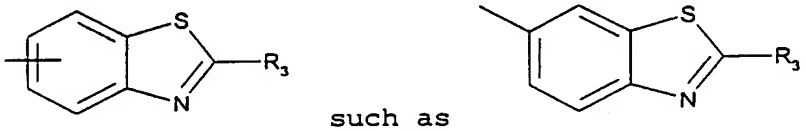


In this group of compounds, R_3 preferably represents hydrogen, hydroxyl or alkylaminocarbonyl.

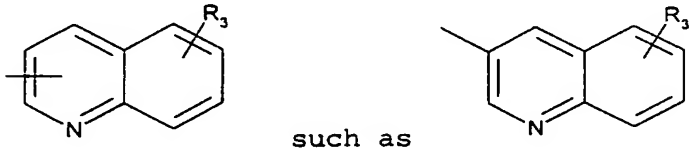
Examples of particular values for Lp in this sub-group are pyrrolidin-1-yl, piperidin-1-yl, 3-N-methyl, N-ethylaminocarbonylpiperidin-1-yl, decahydroisoquinolin-2-yl and 2,3-dihydroindol-1-yl.

Another group of compounds of particular interest is that in which L represents CONH and Lp represents





such as



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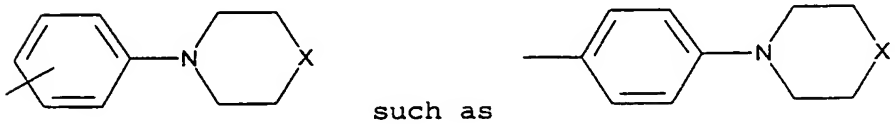

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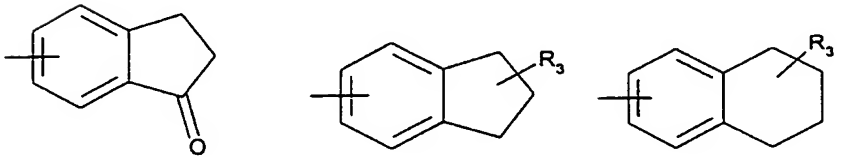
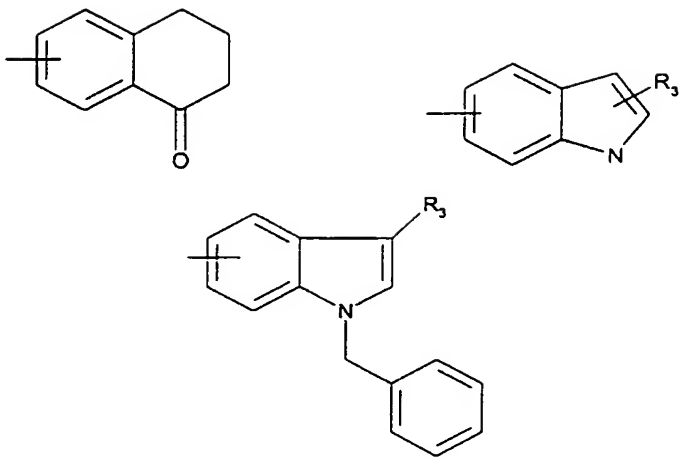




in which X is CH or N.

In this group of compounds, R_3 is preferably hydrogen, amino, hydroxy, alkyl or aminoalkyl.

Examples of particular values are:

(i) 2-aminocyclohexyl or 4-aminomethylcyclohexyl;

(ii) adamantyl;

(iii) 2-aminobenzothiazol-6-yl;

(iv) quinolin-3-yl;

(v) 4-piperidin-1-ylphenyl or 4-piperazin-1-ylphenyl;

(vi) 1-oxoindan-5-yl;

(vii) indan-5-yl;

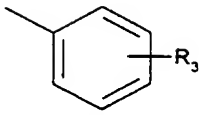
(viii) tetrahydronaphth-6-yl or 1-methyltetrahydronaphth-6-yl;

(ix) 1-oxotetrahydronaphth-6-yl or 1-oxotetrahydronaphth-7-yl;

(x) 2,3-dimethylindol-5-yl; and

(xi) (N-benzyl-3-acetylindol-5-yl or N-benzyl-3-acetylindol-7-yl.

Another group of compounds of particular interest is that in which L represents CONH and Lp represents

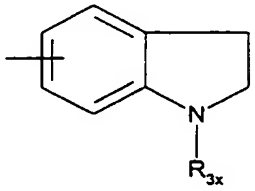


in which R_3 is alkylaminocarbonyl, N-alkylaminoalkanoyl, N-alkanoylaminoalkanonyl, C-hydroxyaminoalkanoyl, hydrogen, alkoxy, alkyl, aminoalkyl, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl, alkylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl.

Preferably the phenyl group is unsubstituted or substituted by one or two R_3 groups.

Examples of particular values are phenyl, 3-cyano-4-methylphenyl, 3-aminocarbonylphenyl, 4-aminocarbonyl-phenyl, 4-chloro-3-aminocarbonyl-phenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 3-aminomethylphenyl, 4-methyl-3-acetylaminophenyl, 4-(1-hydroxethyl)phenyl and 4-isopropylphenyl.

Another particular group of compounds of formula I is that in which L represents CONH and Lp represents



in which R_{3x} represents R_3 or a group of formula

$$-(CO)_p-(G_1)-R_j$$

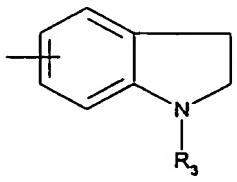
in which p is 0 or 1; G_1 represents (1-3C)alkanediyl or, when p is 1, a bond; and R_j represents a carbocyclic or heterocyclic group, optionally substituted by R_3.

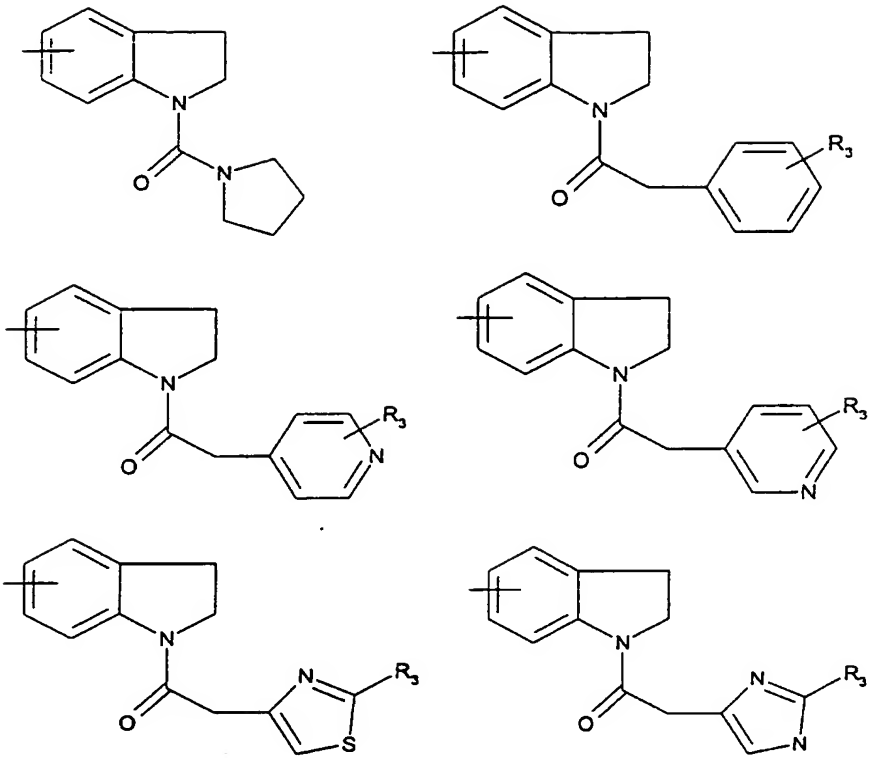
It will be appreciated that when Lp represents a group as described above, it corresponds to a group in which Lp is a combination of a heterocyclic group (2,3-dihydroindolyl), a carbocyclic or heterocyclic group (R_j) and optionally an alkyl group (G_1), which groups are linked by a single bond or a carbonyl group. Accordingly, examples of particular values for R_j are the examples given above for a carbocyclic or heterocyclic group forming part of Lp. Particular mention may be made of pyyrolidinyl, such as pyrrolidin-1-yl, phenyl, thiazolyl, such as thiazol-4-yl, imidazolyl, such as imidazol-4-yl, and pyridyl, such as pyrid-2-yl, pyrid-3-yl and pyrid-4-yl.

Examples of values for G are $-CH_2-$, and CH_2CH_2.

The 2,3-dihydroindolyl group in the above formula is preferably a 2,3-dihydroindol-5-yl or -6-yl group, especially a 2,3-dihydroindol-6-yl group.

Examples of structures of compounds comprising a 2,3-dihydroindolyl group as described above are:





When R_3 is a substituent on the 1-position of a 2,3-dihydroindolyl group, it preferably represents alkylaminocarbonyl; N-alkylaminoalkanoyl; N-alkanoylaminoalkanonyl; C-hydroxyaminoalkanoyl; hydrogen; alkyl; alkanoyl; alkoxycarbonyl; acyloxymethoxycarbonyl; aminoalkyl; aminoalkanoyl; hydroxyalkyl; hydroxyalkanoyl; alkoxyalkyl; or alkanoylamino. Examples of particular values are: N-methylaminoacetyl, N-acetylaminoacetyl, N-acetylalaninoyl, serinoyl, threoninoyl, hydrogen, methyl, acetyl, propanoyl, 2-methylpropanoyl, 3-methylbutyryl, 2-hydroxypropanoyl, hydroxyacetyl, aminoacetyl and alaninoyl.

Accordingly, examples of particular values for Lp are: 1-(N-methylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-acetylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-

acetylalaninoyl)-2,3-dihydroindol-6-yl; 1-(serinoyl)-2,3-dihydroindol-6-yl; 1-(threoninoyl)-2,3-dihydroindol-6-yl; 2,3-dihydroindol-5-yl; 1-methyl-2,3-dihydroindol-6-yl; 1-acetyl-2,3-dihydroindol-6-yl; 1-propanoyl-2,3-dihydroindol-6-yl; 1-(2-methylpropanoyl)-2,3-dihydroindol-6-yl; ; 1-(3-methylbutyryl)-2,3-dihydroindol-6-yl; 1-(2-hydroxpropanoyl)-2,3-dihydroindol-6-yl; 1-hydroxacetyl-2,3-dihydroindol-6-yl; 1-aminoacetyl-2,3-dihydroindol-6-yl and 1-alaninoyl-2,3-dihydroindol-6-yl.

When R_3 is a substituent on a phenyl, thiazolyl, imidazolyl or pyridyl group, it is preferably hydrogen, amino, alkyl or aminoalkyl. Examples of particular values are hydrogen, amino, alkyl or aminomethyl.

Accordingly, further examples of particular values for Lp are: 2,3-dihydroindol-5-yl, 1-prolinoyl-2,3-dihydroindol-6-yl, 1-phenylacetyl-2,3-dihydroindol-6-yl, 1-(2-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(3-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-(3-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-imidazol-4-ylacetyl-2,3-dihydroindol-6-yl, 1-(2-aminothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl, and 1-(2-formamidothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl.

The cyclic group attached to the alpha carbon is preferably an optionally R_{3a} substituted cycloalkyl (such as cyclohexyl), piperidinyl (such as piperidin-4-yl), phenyl, thienyl (such as thien-2-yl or thien-3-yl), thiazolyl (such as thiazol-4-yl or thiazol-5-yl), pyridyl (such as pyrid-3-yl or pyrid-4-yl) or naphthyl (such as naphth-1-yl) group.

Examples of particular values for R_{3a} are:-

hydrogen;

hydroxyl;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxymethyl;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;

for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$, CH_2CONH_2 or aminoacetyl;

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as formylamino or acetylamino;

for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;

amino;

for halo: fluoro or chloro;

cyano;

nitro;

thiol;

for alkylthio: methylthio;

for alkylsulphonyl: methylsulphonyl or ethylsulphonyl;

for alkylsulphenyl: methylsulphenyl;

for imidazolyl: imidazol-4-yl;
hydrazido;
for alkylimidazolyl: 2-methylimidazol-4-yl;
for alkylsulphonamido: methylsulphonylamido or ethylsulphonylamido;
for alkylaminosulphonyl: methylaminosulphonyl or ethylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy; and
for haloalkyl: trifluoromethyl.

Examples of particular values for R_{1C} are:

hydrogen;
hydroxyl;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;
for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as formylamino or acetylamino; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$, CH_2CONH_2 or

aminoacetyl;

Cy is preferably unsubstituted or substituted by one or two R_{3a} groups.

Preferably R_{3a} is hydrogen, hydroxyl, amino, aminomethyl, hydroxymethyl, amido, formylamino, acetylamino or aminoacetyl.

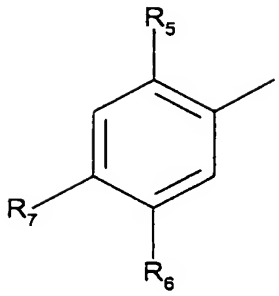
Examples of particular values for Cy are cyclohexyl, piperidin-4-yl, phenyl, 4-aminophenyl, 4-hydroxphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 4-hydroxmethylphenyl, 3-hydroxymethylphenyl, 2-hydroxymethylphenyl, 4-phenylphenyl, 2-aminothiazol-4-yl, 2-formylaminothiazol-4-yl, 2-aminothiazol-5-yl, 2-formylaminothiazol-5-yl, 4-aminopyrid-3-yl, 3-amino-pyrid-4-yl and naphth-1-yl.

Referring to the group R_2, the group R_1 is preferably a group of formula $-CH(R_{6a})NH_2$ in which R_{6a} is hydrogen or methyl. Most preferably it is aminomethyl.

Preferably R_2 represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, substituted in the 3 position by R_1.

The 5 or 6 membered aromatic ring is preferably unsubstituted or substituted in the position alpha to the X-X.. group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio. More preferably it is unsubstituted or substituted by amino. Most preferably it is unsubstituted.

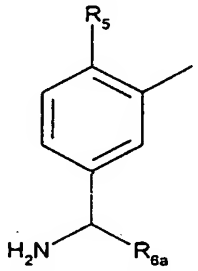
R_2 is preferably a group of formula



wherein R_5 is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R_6 and R_7 which may be the same or different represent hydrogen or R_1.

R_5 is preferably amino or hydrogen. Most preferably it is hydrogen.

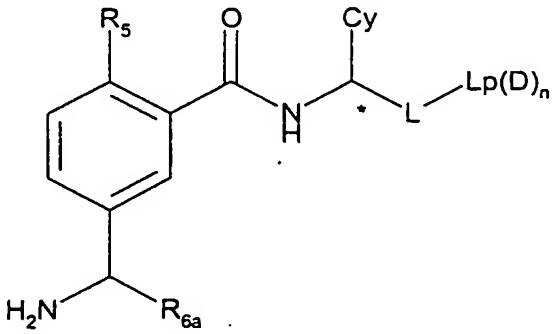
Preferably, R_2 is a group of formula



in which R_5 is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R_{6a} is hydrogen or methyl.

Most preferably, R_2 is 3-aminomethylphenyl.

A group of compounds of particular interest is that of formula



in which:

$L\text{-}Lp(D)_n$ represents $CO\text{-}L_x$;

R_5 represents amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen;

R_{6a} represents hydrogen or methyl;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, hydrazido, alkylsulphonamido, alkylamino-sulphonyl, aminosulphonyl, haloalkoxy, and haloalkyl;

each R_{1c} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

L_x is a mono or bicyclic group bound to the carbonyl via a pendent nitrogen atom or nitrogen atom which forms part of the mono or bicyclic ring;

or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

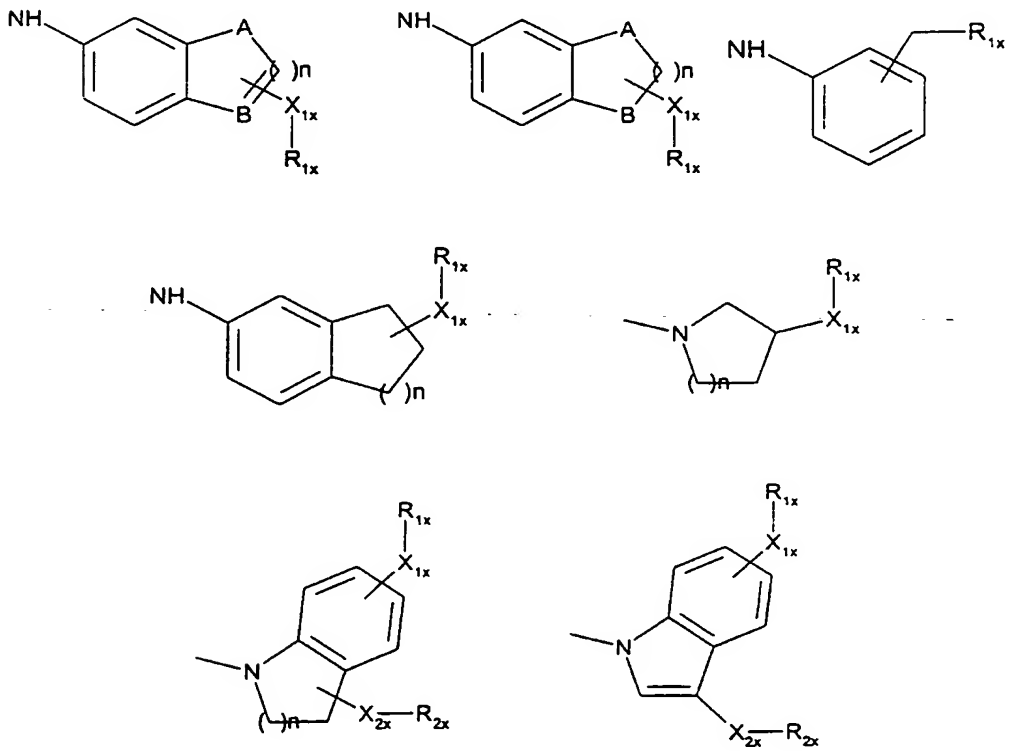
It will be appreciated that when L_x is bound to the carbonyl via a pendant nitrogen, the group $CO\text{-}L_x$ corresponds with the group $L\text{-}Lp(D)_n$ in which L is CONH and Lp is a mono or bicyclic group. When Lx is bound to the carbonyl via a nitrogen that forms part of the mono or bicyclic ring, the group CO-Lx corresponds with the group $L\text{-}Lp(D)_n$ in which L

is CO and Lp is a mono or bicyclic group containing a nitrogen atom in the ring and bound to L via this nitrogen.

It is believed that an aminomethyl group positioned on the 3 position of the phenyl ring will give rise to excellent binding within the S1 binding pocket of tryptase. Without wishing to be limited by theory it is believed that the presence of a hydrogen bond donating group attached to the phenyl group will be essential for successful inhibition of tryptase.

R_5 and R_6 are both preferably hydrogen.

Most preferably the Lx group comprises



wherein:

A and B are independently chosen from NH, N, O, S, CH, CH_2;

X_{1x} and X_{2x} are independently chosen from $(CH_2)_m$, $(CH_2)_mCH=CH(CH_2)_p$, $CO(CH_2)_m$, $NH(CH_2)_m$, $NHCO(CH_2)_m$, $CONH(CH_2)_m$, $SO_2NH(CH_2)_m$, $NHSO_2(CH_2)_m$;

n is 1 or 2;

m is 0 to 2;

p is 0 to 2;

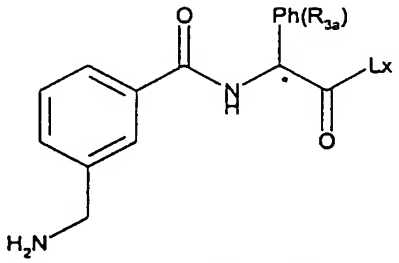
R_{1x} and R_{2x} are independently chosen from hydrogen, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, oxo, heterocyclo optionally substituted by R_{3x}, cycloalkyl optionally substituted by R_{3x} or aryl optionally substituted by R_{3x}; and

R_{3x} is hydrogen, alkoxy, alkyl, amino, hydroxy, alkoxy, alkoxycarbonyl, halo, cyano, nitro, thiol, sulphonyl, or sulphenyl.

Examples of heterocyclic R_{1x} and R_{2x} groups are piperidine, piperazine and pyrrolidine.

The cyclic group attached to the alpha atom is preferably an optionally R_{3a} substituted phenyl.

Thus, one group compounds of the invention are those of formula (II)



* the alpha atom

II

wherein Lx is as hereinbefore defined. It is envisaged that

especially preferred Lx groups will be those in which a cyclic or bicyclic ring is substituted by hydrogen bond donating and/or acceptor groups.

In another embodiment of the invention it is envisaged that the phenyl-based functionality on the left side of the compounds of the invention may be replaced by an optionally substituted, e.g. R substituted, 2-aminomethylthiophene.

The compounds of the invention may be prepared by conventional chemical synthetic routes, e.g. by amide bond formation to couple the aromatic function to the alpha atom and to couple the lipophilic function to the alpha atom. Where the alpha atom is a carbon, the cyclic group-alpha atom combination may conveniently derive from an alpha amino acid (preferably of D configuration) with the aromatic deriving from for example an acid derivative of a compound based on R_2, e.g. an aminomethylbenzoic acid (which is readily available). Amide formation from such reagents (in which any amino or hydroxyl function (especially in an aminomethyl group) may if desired be protected during some or all of the synthesis steps) yields a compound of formula (V).

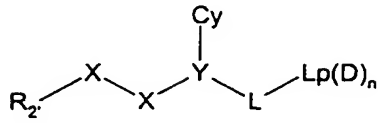
$$R_2\text{-CONH-CH(Cy)-COOH} \qquad (V)$$

(where Cy and R_2 are as defined above).

Prior to reaction the amino group in an aminoalkyl group should be protected by an appropriate protecting group e.g. Boc, Z, Fmoc or Bpoc. The use of protecting groups is described in McOmie, "Protective Groups in Organic Chemistry", Plenum, 1973 and Greene, "Protective Groups in Organic Synthesis", Wiley Interscience, 1981.

According to another aspect therefore, the present

invention provides compounds of formula (I')



(I')

in which R_2, is as defined for R_2 except that the aminoalkyl group R_1 is replaced by a protected aminoalkyl group of formula PG-NH(alkyl)- in which PG ia an amino protecting group (defined in more detail below).

The lipophilic group (and optionally simultaneously the hydrogen bond donor) may then conveniently be introduced by reaction of a compound of formula (V) (or another analogous carboxylic acid) optionally after transformation into an activated form, e.g. an acid chloride or active ester, with a lipophilic group carrying an amine, hydroxylamine, hydrazine or hydroxyl group, e.g. to produce compounds with linkages of $-CO-NR_1-$, $-CO-NR_{1d}-O-$, $-CO-NR_{1d}-NR_{1d}-$ and $-CO-O-$ from the alpha atom (where it is a carbon) to the lipophilic group. If necessary the amide linkage can be reduced using an appropriate reducing agent employing the necessary protection depending on whether concurrent reduction of the carboxylic acid moiety is also desired. Alternatively a compound of formula V or another analogous carboxylic acid may be transformed into an alcohol by reaction with isobutylchloroformate and reduction with sodium borohydride.

Such an alcohol, e.g. of formula (VI)

$$R_2 - CONH - CH(Cy)CH_2OH \qquad (VI)$$

can be reacted to introduce the lipophilic group by reactions such as:

alkylation with an alkyl halide in the presence of a

base;

reaction under Mitsunobu conditions, such as with diethyl azodicarboxylate/triphenylphosphine and a hydroxylated aryl compound;

by reaction with an activated carboxylic acid (e.g. an acid chloride) or with a carboxylic acid and diethylazodicarboxylate/triphenylphosphine;

by reaction with an isocyanate; and

by treatment with methanesulphonyl chloride or trifluoromethanesulphonic anhydride and reaction with an amine, or with a thiol optionally followed by oxidation, e.g. with potassium metaperiodate or hydrogen peroxide.

In this way compounds with linkages of $-CH_2-O-$, $-CH_2-O-CO-$, $-CH_2-O-CO-NR_{1d}-$, $-CH_2-NR_{1d}-$, $-CH_2-S-$, $-CH_2-SO-$ and $-CH_2-SO_2-$ between the alpha carbon and the lipophilic group may be produced.

Alternatively the alcohol can be oxidized to form a corresponding aldehyde (e.g. by oxidation with manganese dioxide or DMSO/oxalyl chloride or DMSO/SO_3 or Dess-Martin reagent) which may be reacted to introduce the lipophilic group by reactions such as:

reaction with Wittig reagents or Horner-Emmons reagents, optionally followed by reduction of the resulting carbon:carbon double bond using H_2/Pd-carbon;

reaction with an organometallic, eg a Grignard reagent, optionally followed by reaction on the resulting hydroxyl group, such as oxidation (eg with MnO_2, DMSO/oxalyl chloride or Dess-Martin reagent), alkylation (eg with an alkyl halide in the presence of a base in a solvent such as DMF), arylation (eg with diethylazo dicarboxylate/triphenyl

phosphine and a hydroxyaryl compound), ester formation (eg with an acid chloride or with a carboxylic acid and diethylazido dicarboxylate/triphenyl phosphine), or carbamate formation (eg with an isocyanate);

by reaction with an amine followed by reduction, e.g. with sodium cyanoborohydride;

by reaction with a hydrazine; or

by reaction with a carbazide.

In this way compounds with linkages of $-CH=CR_{1d}-$, $-CH_2-CHR_{1d}-$, $-CHOH-$, $-CHR_{1d}-O-$, $-CHR_{1d}-O-CO-$, $-CHR_{1d}-O-CO-NR_{1d}-$, $-CO-$, $-CH_2-NR_{1d}-$, $-CH=N-NR_{1d}-$ and $-CH=N-NR_1-CO-NR_{1d}-$ between the alpha carbon and the lipophilic group may be produced.

The transformation of alcohol to amine referred to above may be used to produce an amine reagent for lipophilic group introduction, e.g. a compound

$$R_2-CONH-CH(Cy)-CH_2-NR_{1d}H.$$

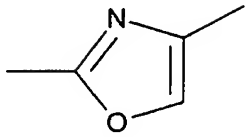
Such an amine reagent may be reacted to introduce the lipophilic group, e.g. by acylation with an acid halide or activated ester, by reaction with isocyanate, by reaction with an isothiocyanate, or by reaction with a sulphonyl chloride. In this way compounds with linkages of $-CH_2NR_{1d}-CO-$, $-CH_2-NR_{1d}-CO-NR_{1d}-$, $-CH_2NR_{1d}-CS-NR_{1d}-$ and $-CH_2NR_{1d}-SO_2-$ between the alpha carbon and the lipophilic groups may be produced.

The transformation of acid to amide referred to above may be used to produce an amide reagent for introduction of the lipophilic group, e.g. a compound

$$R_2-CONH-CH(Cy)-CON(R_{1d})_2.$$

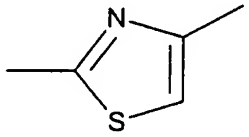
Such amides may be reacted to introduce lipophilic groups, e.g. by reaction with a haloketone (e.g. phenacyl

bromide). This provides a linkage

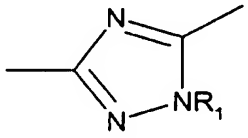


from alpha carbon to lipophilic group.

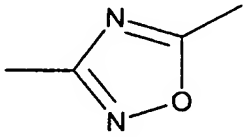
Analogously the amide may be transformed to a thioamide by reaction with Lawesson's reagent and then reacted with a haloketone to form a linkage



The amide reagent may likewise be transformed to a nitrile reagent by dehydration, e.g. with trifluoroacetic anhydride. The nitrile reagent may be reacted with hydrazine then with acyl halide and then cyclized, (e.g. with trifluoroacetic anhydride) to produce a linkage



Alternatively it may be treated with hydroxylamine then reacted with acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce a linkage

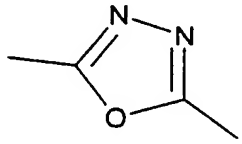


The hydrazide produced by reaction of a carboxylic acid reagent with hydrazine discussed above may likewise be used as a reagent for lipophilic group introduction, e.g. as a

compound of formula

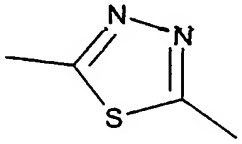
$$R_2\text{-}CONH\text{-}CH(Cy)\text{-}CO\text{-}NR_{1d}\text{-}N\ (R_{1d})_2.$$

Thus the hydrazide reagent can be reacted with an acyl halide and cyclized, e.g. with trifluoroacetic anhydride to yield a linkage

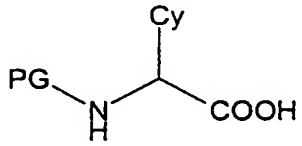


or reacted with an acyl halide or an isocyanate to yield linkages $-CO\text{-}NR_1\text{-}NR_{1d}\text{-}CO-$ and $-CO\text{-}NR_{1d}\text{-}NR_{1d}\text{-}CO\text{-}NR_{1d}-$ respectively.

Alternatively the hydrazide may be transformed by reaction with Lawesson's reagent and then reacted with an acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce the linkage



An alternative route to these compounds is to carry out any of the above chemical reactions to incorporate the lipophilic group (an optional H bond donor) into a protected intermediate such as a compound of formula (VII).



PG = Protecting group

The protecting group may then be removed before coupling of the for example o-amino benzoic acid (optionally protected).

The protection of amino and carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include C_1-C_6 alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aryl(C_1-C_4)alkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups (PG) include acyl groups, such as groups of formula RCO in which R represents C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy, or a C_{3-10} cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, C_1-C_4 alkyl and C_1-C_4 alkoxy. Preferred amino protecting groups include t-butoxycarbonyl (Boc) and benzyl.

α-Amino acids of formula (VII) which are not commercially available can be synthesized by methods known in the art, for example as described in "Synthesis of Optically Active α-Amino Acids" by Robert M. Williams (Pergamon Press, 1989) and "Asymmetric Synthesis of ArylGlycines", Chem. Rev. 1992, 889-917.

Compounds of the type (VII) made be prepared (for example) by one or more of the following methods.

(i) from aryl or heteroaryl aldehydes via the Strecker synthesis or modifications thereof, via Bucherer-Bergs

hydantoin synthesis, or via the Ugi methodology (Isonitrile Chemistry, Ugi I. Ed.; Academic: New York, 1971; pp145-199) with removal and replacement of protecting groups;

(ii) from styrenes via Sharpless methodology (J. Am. Chem. Soc. 1998,120, 1207-1217)

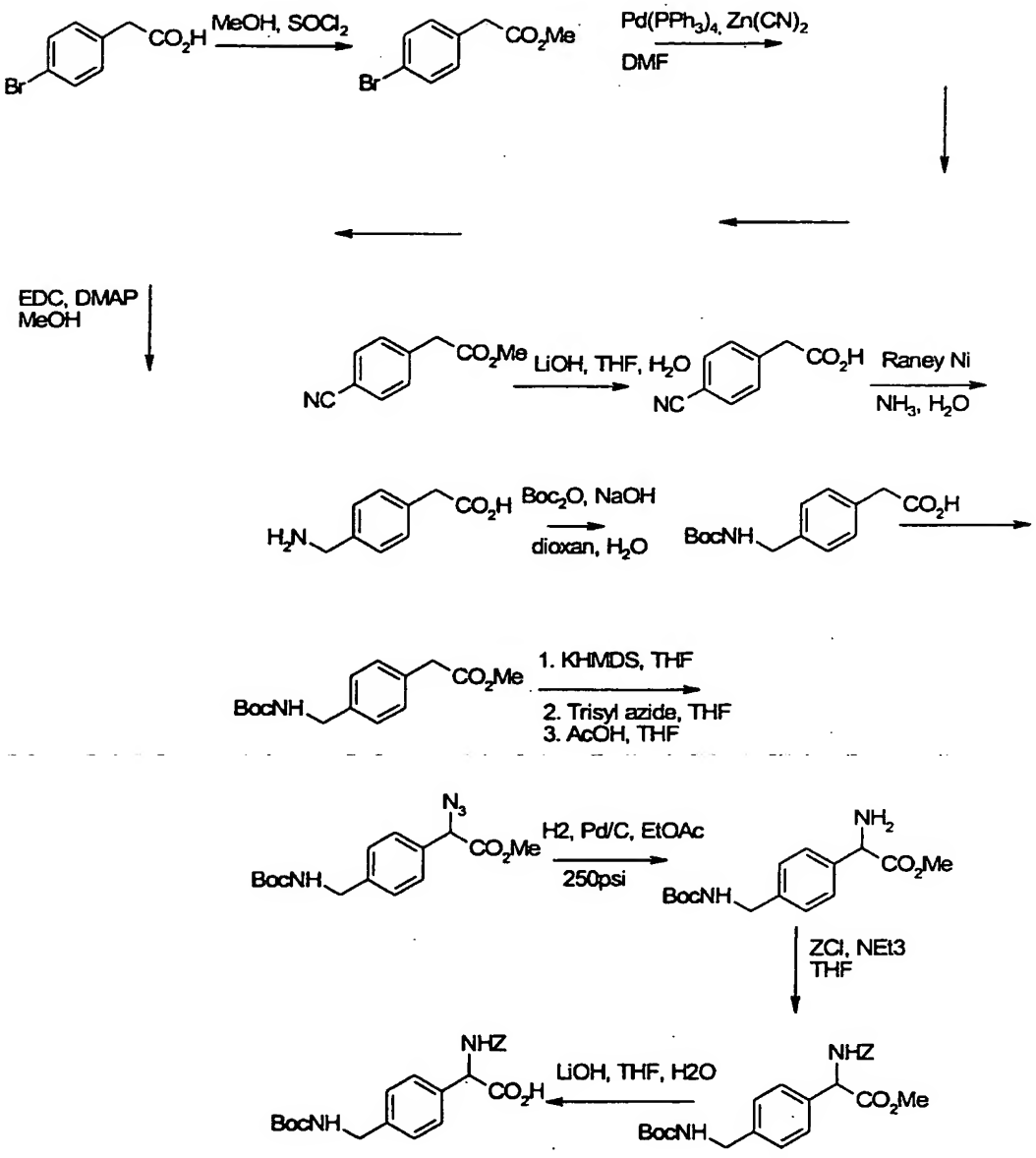
(iii) from aryl boronic acids via Petasis methodology (Tetrahedron, 1997, 53, 16463-16470) with removal and replacement of protecting groups;

(iv) from aryl and heteroaryl acetic acids - via Evan's azidation (Synthesis, 1997, 536-540) or by oximation, followed by reduction and addition of protecting groups;

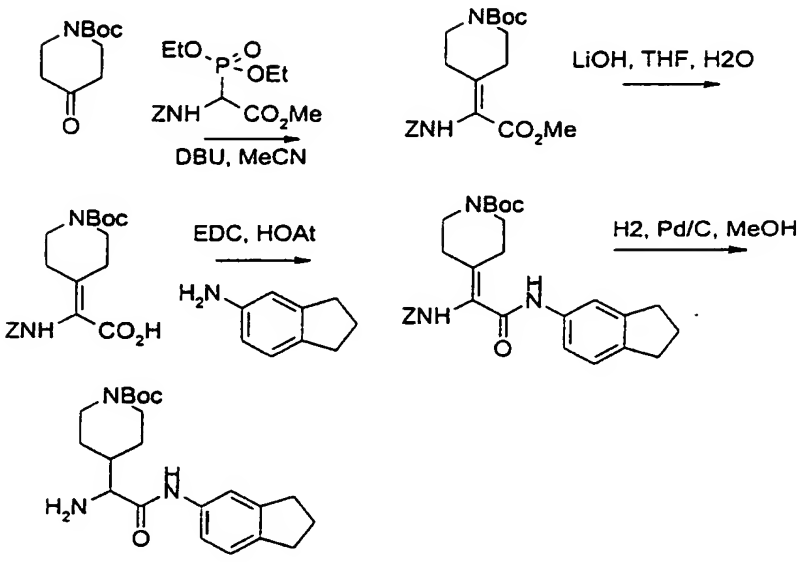
(v) from existing aryl glycines by manipulation of functional groups, for example, alkylation of hydroxy groups, palladium assisted carbonylation of triflates derived from hydroxy groups and further manipulation of the carboxylic esters to give carboxylic acids by hydrolysis, carboxamides by activation of the carboxylic acid and coupling with amines, amines via Curtius reaction on the carboxylic acid; or

(vi) from aliphatic, carbocylic and non-aromatic heterocyclic aldehydes and ketones using a Horner-Emmons reaction with N-benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (Synthesis, 1992, 487-490).

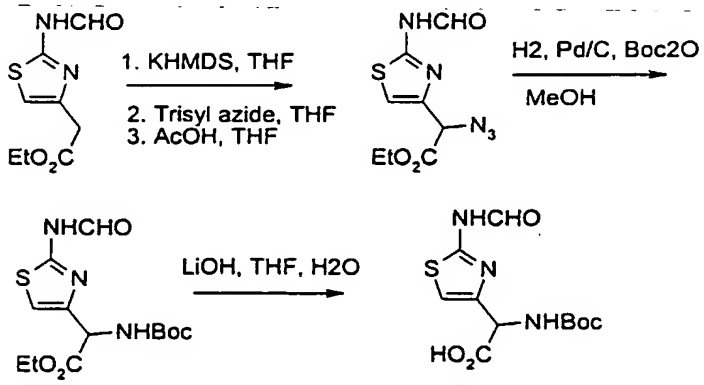
Examples of synthetic schemes are shown below:


MeOH, SOCl2
Pd(PPh3)4, Zn(CN)2
DMF
EDC, DMAP
MeOH
LiOH, THF, H2O
Raney Ni
NH3, H2O
Boc2O, NaOH
dioxan, H2O
1. KHMDS, THF
2. Trisyl azide, THF
3. AcOH, THF
H2, Pd/C, EtOAc
250psi
ZCl, NEt3
THF
LiOH, THF, H2O

Synthesis of protected 4-piperidylglycine

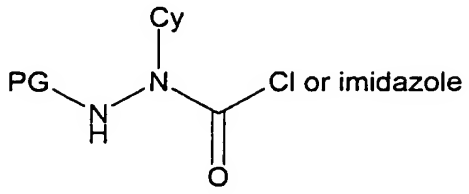


Synthesis of protected 2-aminothiaz-4-ylglycine



A starting reagent for lipophilic group introduction where the alpha atom is nitrogen may be produced for example by reaction of a beta protected hydrazine (such protection to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene,

triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type:



PG = Protecting group

This intermediate may be used as has been described above for the carboxylic starting reagents where the alpha atom is carbon.

Removal of the protecting group by standard methods and coupling with an activated aryl carboxylic acid will give compounds of the type

$$R_2\text{-}CONH\text{-}N(Cy)\text{-}L\text{-}Lp(D)_n$$

(where R_2, X, Y, Cy, L, Lp and D are as defined above).

Thus viewed from a further aspect the invention provides a process for the preparation of a compound according to the invention which process comprises coupling a lipophilic group to a compound of formula (VIII)

$$R_2\text{-}(X)_2\text{-}Y(Cy)\text{-}Z_1 \qquad (VIII)$$

(wherein R_2, X, Y and Cy are as defined above and Z_1 is a reactive functional group), and optionally subsequently coupling a hydrogen bond donor group to said lipophilic group.

Instead of introducing the group $L\text{-}Lp(D)_n$ as the final stage process step, the compounds of formula I may

alternatively be prepared by a process in which the group R_2 is introduced in the final process step.

Thus viewed from another aspect the invention provides a process for the preparation of a compound according to the invention which process comprises coupling a lipophilic group to a compound of formula (IX)

$$Z_2\text{-}Y(Cy)\text{-}L\text{-}Lp(D)_n \qquad (IX)$$

(wherein Y, Cy, L, Lp D, and n are as defined above and Z_2 is HX or a reactive functional group), or a protected derivative thereof, with a compound of formula (X)

$$R_2\text{-}\ Z_3$$

(wherein R_2 is as defined above and Z_3 is XH or an appropriate reactive group), or a protected derivative thereof, followed if necessary by the removal of any protecting groups.

Thus, for a compound of formula I in which X-X represents CONH, a compound of formula (IX) in which Z_2 is H_2N may be reacted with a compounds of formula (X) in which Z_3 is COOH or a reactive derivative thereof, such as a acyl halide or an anhydride, for example as described in the Examples herein.

Where the lipophilic group Lp comprises more than one group, it may generally be formed by coupling these groups together at an appropriate stage in the preparation of the compound of formula I using conventional methods or as described in the Examples.

The compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or

vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

The following are examples of pharmaceutical compositions of compounds according to the invention.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on

a tablet machine to yield tablets each weighing 150 mg.

In particular, it is believed that the compounds of the invention will have excellent oral bioavailability.

Viewed from this aspect the invention provides a pharmaceutical composition comprising a serine protease (tryptase) inhibitor according to the invention together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further anti-inflammatory

Viewed from a further aspect the invention provides the use of a serine protease (tryptase) inhibitor according to the invention for the manufacture of a medicament for use in a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

Viewed from a further aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a serine protease (tryptase) inhibitor.

The dosage of the inhibitor compound of the invention will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

All publications referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples.

Experimental:

Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are HPLC, high-performance liquid chromatography; LC/MS, liquid chromatography / mass spectrometry; rt, retention time; NMR, nuclear magnetic resonance, TBTU, 2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate. Starting materials were purchased from Aldrich (Gillingham, UK), Lancaster (Morecambe, UK), Avocado (Heysham, UK), Maybridge (Tintagel, UK), Nova Biochem (Nottingham, UK) or Bachem.

Purification:

Flash column chromatography was carried out using Merck silica gel Si60 (40-63 μm, 230-400 mesh). Purification of final products was by crystallisation, flash column chromatography or gradient reverse phase HPLC on a Waters Deltaprep 4000 at a flow rate of 50 mL/minute using a Deltapak-C18 radial compression column (40 mm x 210 mm, 10-15 mm particle size). Eluant A consisted of aqueous trifluoroacetic acid (0.1 %) and eluant B 90% acetonitrile in aqueous trifluoroacetic acid (0.1 %) with gradient elution (Gradient, 0 minutes 5 % B for 1 minutes, then 5 % B to 20 % B over 4 minutes, then 20 % B to 60 % B over 32 minutes). Fractions were analysed by analytical HPLC and LC/MS before pooling those with >95 % purity for lyophilisation.

Analysis:

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DPX300 (300 MHz). Analytical HPLC's

were performed on a Shimadzu LC6 gradient system equipped with an autosampler. Eluant A consisted of aqueous trifluoroacetic acid (0.1 %) and eluant B consisted of 90 % acetonitrile and 10 % water, containing trifluoroacetic acid (0.1 %). Gradient 1 elution began at 5 % B and increased to 100 % B over seven minutes. Gradient 2 elution began at 5 % B and increased to 100 % B over ten minutes. Gradient 3 elution began at 5 % B for one minute, increasing to 20 % B after the fourth minute, 40 % B after the 14th minute and then 100 % B after the 15th minute. The columns used were Luna 2 C18 (3 μ, 30 mm x 4.6 mm), Luna 2 C18 (5 μ, 150 mm x 2 mm) and a Symmetry Rp8 (3.5 μ, 50 x 2.1 mm).

LC/MS were performed on a PESCIEX single quadrupole API-150EX instrument, equipped with a Luna 2 C18 column (3 μ, 30 mm x 4.6 mm) eluting with 20 % to 100 % acetonitrile in water over five minutes.

Example 1

3-(Aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide bis(trifluoroacetate) salt

2,6-Diaminobenzothiazole

2-Amino-6-nitrobenzothiazole (500 mg, 2.56 mmol) was dissolved in methanol (20 mL) and 10 % palladium on carbon (50 mg) was added as a slurry in methanol (1 mL). The atmosphere was replaced with hydrogen and the suspension was stirred overnight. The catalyst was removed by suction filtration and the solvent evaporated to afford 2,6-diaminobenzothiazole (420 mg, 99 %) as a pale yellow solid.

***N*-BOC-D-Phenylglycine 2-aminobenzothiazol-6-amide**

N-BOC-D-Phenylglycine (250 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg, 1.0 mmol) and 7-aza-1-hydroxybenzotriazole (140 mg, 1.0 mmol) were stirred in dimethylformamide (3 mL) for ten minutes. 2,6-Diaminobenzothiazole (160 mg, 1.0 mmol) was then added and the solution was stirred overnight at room temperature. Ethyl acetate (15 mL) was added and the solution was washed with water (5 mL), saturated citric acid solution (5 mL), saturated $NaHCO_3$ (5 mL) and water (5 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford *N*-BOC-D-phenylglycine 2-aminobenzothiazol-6-amide.

^1H NMR ($CDCl_3$): 8.93 (1 H, br s, C(O)NHAr); 7.72 (1 H, s, benzothiazole C(7)H); 7.35 (2 H, br s, Ph); 7.23 - 7.05 (3 H, m, Ph); 6.93 (1 H, d, J = 10 Hz, benzothiazole C(4)H or

C(5)H); 6.72 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 6.05 (1 H, d, J = 7 Hz, CHPh); 5.92 (2 H, br s, NH_2); 5.45 (1 H, br s, BOCNH); 1.27 (9 H, s, ^tBu).

D-Phenylglycine 2-aminobenzothiazol-6-amide

A solution of *N*-BOC-D-phenylglycine 2-aminobenzothiazol-5-amide in dichloromethane (5 mL) was treated with trifluoroacetic acid (5 mL) and stirred for 30 minutes. The dichloromethane and excess trifluoroacetic acid were removed under reduced pressure and the residue was triturated with diethyl ether to afford D-phenylglycine 2-aminobenzothiazol-6-amide as its trifluoroacetate salt (350 mg, 89 %).

3-(Aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide trifluoroacetate salt

N-BOC-3-aminomethylbenzoic acid (250 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg, 1.0 mmol) and 7-aza-1-hydroxybenzotriazole (140 mg, 1.0 mmol) were stirred in dimethylformamide (10 mL) for five minutes. D-Phenylglycine 2-aminobenzothiazol-6-amide trifluoroacetate salt (350 mg, 0.85 mmol) was then added and the mixture was stirred overnight. The solution was poured into ethyl acetate (20 mL) and washed with 5 % HCl (5 mL), saturated $NaHCO_3$ (5 mL) and water (5 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (60 % ethyl acetate / 40 % hexane to 100 % ethyl acetate) to afford *N*-BOC-3-(aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide. This was dissolved in dichloromethane (5 mL) and trifluoroacetic acid

(5 mL) was added. The solution was stirred at room temperature for 30 minutes before the dichloromethane and excess trifluoroacetic acid were removed under reduced pressure. The residue was triturated with diethyl ether to afford 3-(aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide as its trifluoroacetate salt (150 mg, 32 %).

^{1}H NMR (d_4 MeOH): 8.21 ppm (1 H, s, benzothiazole C(7)H); 7.97 (1 H, s, aminomethylbenzoyl C(2)H); 7.94 (1 H, d, J = 5 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.80 - 7.48 (5 H, m, Ar); 7.47 - 7.32 (4 H, m, Ar); 5.81 (1 H, s, C<u>H</u>Ph); 4.22 (2 H, s, $C\underline{H}_2NH_2$).

HPLC (Luna 2, Gradient 1): rt = 2.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.40 minutes, 432 $(MH)^+$.

Examples 2 - 34 were prepared in the same fashion as Example 1, starting with the indicated nitro-compound or amine. Other functional groups present were protected appropriately.

Example 2

3-(Aminomethyl)benzoyl-D-phenylglycine phenylamide trifluoroacetate salt

Prepared from aniline.

^{1}H NMR (d_4 MeOH): 7.85 ppm (2 H, br s, Ar); 7.49 (6 H, m, Ar); 7.27 (5 H, m, Ar) 7.01 (1 H, t, *J* = 9 Hz, Ar); 5.70 (1 H, s, C<u>H</u>Ph); 4.12 (2 H, s, $\underline{C}H_2NH_2$).

HPLC (Luna 2, Gradient 1): rt = 3.59 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.99 minutes, 360 $(MH)^+$.

Example 3

2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine *(1S,2S,3S,5R)*-isopinocamphamide dihydrochloride salt

Prepared from *(1S,2S,3S,5R)*-(+)-isopinocampheylamine.

^{1}H NMR (d4 MeOH): 7.52 ppm (1 H, s, Ar-C(6)H); 7.42 (2 H, d, J = 10, 2 x Ph-*o*-CH); 7.32 - 7.2 (3 H, m, 2 x Ph-*m*-CH, Ph-*p*-CH); 7.12 (1 H, d, J = 11 Hz, Ar-C(4)H); 6.67 (1 H, d, J = 11 Hz, Ar-C(3)H); 5.53 (1 H, s, NC<u>H</u>(Ph)); 4.18 (1 H, quintet, J = 8 Hz, ipc-C(1)H); 3.90 (2 H, s, $C\underline{H}_2NH_2$); 2.42 - 2.23 (2 H, m, ipc-C(3)H and ipc-(C(2)H); 1.91 (1 H, m, ipc-(C)6H); 1.80 (1 H, br s, ipc-(C)5H); 1.74 (1 H, t, J = 5 Hz, ipc-(C)6H); 1.32 (1 H, dd, J = 14, 8 Hz, ipc-C(7)H); 1.14 (3 H, s, ipc-C(8)H_3); 1.02 (3 H, d, J = 8 Hz, ipc-C(10)H_3); 0.95 (3 H, s, ipc-C(9)H_3); 0.87 (1 H, d, J = 11 Hz, ipc-C(7)H).

HPLC (Luna 2, Gradient 1): rt = 4.21 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 418 $(MH-NH_3)^+$.

Example 4

3-(Aminomethyl)benzoyl-D-phenylglycine quinolin-3-ylamide trifluoroacetate salt

Prepared from 3-aminoquinoline.

^{1}H NMR (d_4 MeOH): 9.21 and 8.88 ppm (1 H each, s, quinoline C(2)H and C(4)H); 8.10 - 7.90 (4 H, m, Ar); 7.81 (1H, t, J = 7 Hz, Ar); 7.77 - 7.55 (5 H, m, Ar); 7.53 - 7.25 (3 H, m, Ar); 5.91 (1 H, s, C<u>H</u>Ph); 4.20 (2 H, s, CH_2NH_2).

HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 411 $(MH)^+$.

Example 5

3-(Aminomethyl)benzoyl-D-phenylglycine 4-(1-piperidyl)phenylamide trifluoroacetate salt

Prepared from 4-(1-piperidyl)aniline.

^{1}H NMR (d_4 MeOH): 7.97 ppm (2 H, m, Ar); 7.8 (2 H, d, J = 9 Hz, Ar); 7.7 - 7.35 (9 H, m, Ar); 5.8 (1 H, s, C<u>H</u>Ph); 4.2 (2 H, s, <u>C</u>H_2NH_2); 3.55 (4 H, m, pip); 2.0 (4 H, m, pip); 1.8 (2 H, m. pip).

HPLC (Luna 2, Gradient 1): rt = 2.81 minutes

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 443 $(MH)^+$

Example 6: 3-(Aminomethyl)benzoyl-D-phenylglycine 1-oxoindan-5-amide trifluoroacetate salt

Prepared from 5-amino-1-oxoindane.

^{1}H NMR (d_4 MeOH): 7.98 ppm (1 H, s, (aminomethyl)benzoyl C(2)H); 7.96 ppm (1 H, d, J = 10 Hz, (aminomethyl)benzoyl C(6)H); 7.94 (1 H, s, indanone C(4)H); 7.70 - 7.52 (6 H, m, Ar); 7.47 - 7.33 (3 H, m, Ar); 5.84 (1 H, s, C<u>H</u>Ph); 4.22 (2 H, s, CH_2NH_2); 3.12 (2 H, t, J = 5 Hz, indanone C(3)H_2); 2.82 - 2.75 (2 H, m, indanone C(2)H_2).

HPLC (Luna 2, Gradient 1): rt = 3.35 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 414 $(MH)^+$.

Example 7

3-(Aminomethyl)benzoyl-D-phenylglycine 3-cyano-4-methylphenyl-amide trifluoroacetate salt

Prepared from 3-cyano-4-methylaniline.

^{1}H NMR (d_4 MeOH): 8.01 ppm (1 H, s, 3-cyano-4-methylphenyl C(2)H); 7.98 (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d, J = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.72 - 7.52 (5 H, m, Ar); 7.48 - 7.28 (4 H, m, Ar); 5.82 (1 H, s, C<u>H</u>Ph);

4.19 (2 H, s, CH_2NH_2); 2.47 (3 H, s, CH_3).

HPLC (Luna 2, Gradient 1): rt = 3.72 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 399 $(MH)^+$.

Example 8

3-(Aminomethyl)benzoyl-D-phenylglycine 4-amido phenylamide trifluoroacetate salt

Prepared from 4-nitrobenzamide.

^1H NMR (d_4 MeOH): 8.20 - 8.05 ppm (2 H, m, 3-(aminomethyl)benzoyl C(2)H and C(6)H); 7.97 (2 H, d, J = 9 Hz, 4-(amidocarbonyl)phenyl C(2)H and C(6)H); 7.86 (2 H, d, J = 9 Hz, 4-(amidocarbonyl)phenyl C(3)H and C(5)H); 7.82 - 7.65 (4 H, m, Ar); 7.63 - 7.47 (3 H, m, Ar); 6.01, (1 H, s, CHPh); 4.32 (2 H, br s, CH_2NH_2).

HPLC (Symmetry C8, Gradient 2): rt = 4.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.51 minutes, 403 $(MH)^+$.

Example 9

3-(Aminomethyl)benzoyl-D-phenylglycine 3-amidophenylamide trifluoroacetate salt

Prepared from 3-nitrobenzamide.

^1H NMR (d_4 MeOH): 8.30 ppm (1, s, 3-(amidocarbonyl)phenyl C(2)H); 8.17 (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.12 (1 H, d, J = 8 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.93 (1 H, d, J = 7 Hz, 3-(amidocarbonyl)phenyl C(6)H); 7.85 - 7.68 (5 H, m, Ar); 7.65 - 7.52 (4 H, m, Ar); 6.03 (1 H, s, CHPh); 4.37 (2 H, br s, CH_2NH_2).

HPLC (Luna 2, Gradient 1): rt = 2.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 403 $(MH)^+$.

Example 10

3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-tetrahydro-1-oxonaphthyl-6-amide trifluoroacetate salt.

Prepared from 6-amino-1,2,3,4-tetrahydro-1-oxonaphthalene.

^{1}H NMR (d_4 MeOH): 7.72 ppm (3 H, m, Ar); 7.40 (6 H, m, Ar); 7.20 (3 H, m, Ar); 5.65 (1 H, s, C<u>H</u>Ph); 4.02 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.78 (2 H, t, J = 6 Hz, tetrahydronaphthyl C(4)H$_2$); 2.42 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(2)H$_2$); 1.95 (2H, m, tetrahydronaphthyl C(3)H$_2$).

HPLC (Luna 2, gradient 1): rt = 3.57 minutes.

LC/MS (Luna 2, gradient 4): rt = 1.88 minutes; 428 $(MH)^+$.

Example 11

3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-tetrahydro-1-oxonaphthyl-7-amide trifluoroacetate salt

Prepared from 7-nitro-1,2,3,4-tetrahydro-1-oxonaphthalene.

^{1}H NMR (d_4 MeOH): 8.04 ppm (1 H, s, tetrahydronaphthyl C(8)H); 7.82 (2 H, dd, J = 1, 10 Hz, Ar); 7.60 (2 H, dd, Ar); 7.45 (4 H, m, Ar); 7.28 (3 H, m, Ar); 7.16 (1 H, m, Ar); 5.68 (1 H, br s, C<u>H</u>Ph); 4.03 (2 H, s, C<u>H</u>$_2$NH$_2$), 2.83 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(4)H$_2$); 2.40 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(2)H$_2$); 2.00 (2 H, m, tetrahydronaphthyl C(3)H$_2$).

HPLC (Luna 2, gradient 1): rt = 3.65 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.94 minutes, 428 $(MH)^+$.

Example 12

3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-tetrahydro-naphthyl-6-amide trifluoroacetate salt

Prepared from 6-amino-1,2,3,4-tetrahydronaphthalene.

^{1}H NMR (d_4 MeOH): 7.72 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.70 (1 H, d, J = 7 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.40 (4 H, m, Ar); 7.22 (3 H, m, Ar); 7.09 (1 H, m, Ar); 6.82 (1 H, m, Ar); 5.62 (1 H, s, C<u>H</u>Ph); 4.00 (2 H, s, $C\underline{H}_2NH_2$); 2.50 (4 H, s,); 1.58 (4 H, s, tetrahydronaphthyl C(4)H_2 and C(5)H_2).

HPLC (Luna 2, Gradient 4): rt = 4.21 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.21 minutes, 414 $(MH)^+$.

Example 13

3-(Aminomethyl)benzoyl-D-phenylglycine 4-(piperazin-1-yl)phenyl-amide bis(trifluoroacetate) salt

Prepared from 4-(piperazin-1-yl)aniline.

^{1}H NMR (d_4 MeOH): 8.00 ppm (2 H, m, Ar); 7.70 - 7.35 (9 H, m, Ar); 7.02 (2 H, d, J = 10 Hz, Ar); 5.80 (1 H, s, C<u>H</u>Ph); 4.21 (2 H, s, CH_2NH_2); 3.30 (8 H, m, pip).

HPLC (Luna 2, Gradient 1): rt = 2.71 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 444 $(MH)^+$.

Example 14

3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol 5-amide bis(trifluoroacetate) salt

Prepared from 2,3-dihydro-5-nitroindole.

^{1}H NMR (d_4 MeOH): 7.97 ppm (2 H, m, Ar); 7.82 (1 H, s, Ar); 7.65 (5 H, m, Ar); 7.45 (4 H, m, Ar); 5.80 (1 H, s, C<u>H</u>Ph); 4.20 (2 H, s, $C\underline{H}_2NH_2$); 3.85 (2 H, t, J = 7.5 Hz, dihydroindole C(2)$\underline{H}_2$); 3.30 (2 H, t, J = 7.5 Hz, dihydroindole C(3)$\underline{H}_2$).

HPLC (Luna 2, Gradient 1): rt = 2.59 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 401 $(MH)^+$.

Example 15

3-(Aminomethyl)benzoyl-D-phenylglycine 4-chloro-3-amidophenylamide trifluoroacetate salt

Prepared from 2-chloro-5-nitrobenzamide.

^{1}H NMR (d_4 MeOH): 7.98 ppm (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d, J = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.83 (1 H, s, 2-chloro-3-(amidocarbonyl)-phenyl C(6)H); 7.70 - 7.50 (5 H, m, Ar); 7.45 - 7.35 (4 H, m, Ar); 5.58 (1 H, s, C<u>H</u>Ph); 4.21 (2 H, s, C<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 3.09 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.62 minutes, 437/439 $(MH)^+$.

Example 16

3-(Aminomethyl)benzoyl-D-phenylglycine 3,5-dichlorophenylamide trifluoroacetate salt

Prepared from 3,5-dichloroaniline.

^{1}H NMR (d_4 MeOH): 7.98 ppm (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d, J = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.73 - 7.51 (4 H, m, Ar); 7.64 (2 H, s, 3,5-dichlorophenyl C(2)H and C(6)H); 7.49 - 7.32 (3 H, m, Ar); 7.18 (1 H, s, 3,5-dichlorophenyl C(4)H); 5.80 (1 H, s, C<u>H</u>Ph); 4.20 (2 H, s, CH$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.31 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.29 minutes, 428/430/432 $(MH)^+$.

Example 17

3-(Aminomethyl)benzoyl-D-phenylglycine 3-

(aminomethyl)phenyl-amide bis(trifluoroacetate) salt

Prepared from 3-nitrobenzylamine.

^{1}H NMR (d_4 MeOH): 7.97 ppm (2 H, m Ar); 7.82 (1 H, s, Ar); 7.61 (5 H, m, Ar); 7.40 (4 H, m, Ar); 7.22 (1 H, d, J = 11 Hz, Ar); 5.81 (1 H, s, C<u>H</u>Ph); 4.22 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.10 (2 H, s, C<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 2.67 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 389 $(MH)^+$.

Example 18

3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dimethylindol-5-amide bis(trifluoroacetate) salt

Prepared from 2,3-dimethyl-5-nitroindole.

^{1}H NMR (d_3 acetonitrile): 9.12 ppm (1 H, br s, NH); 9.08 (1H, bs, NH); 8.40 (1 H, d, J = 7 Hz, Ar), 8.20 (1 H, s, Ar); 8.0 (1 H, d, J = 7 Hz, Ar); 7.88-7.50 (7 H, m, Ar); 7.30 (2 H, m, Ar); 6.0 (1 H, d, J = 6.5 Hz, C<u>H</u>Ph); 4.30 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.71 (2 H, br s, CH$_2$N<u>H</u>$_2$); 2.50 (3 H, s, indole C(3)C<u>H</u>$_3$); 2.31 (3 H, s, indole C(2)C<u>H</u>$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.76 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.99 minutes, 427 $(MH)^+$.

Example 19

3-(Aminomethyl)benzoyl-D-phenylglycine 4-chlorophenylamide trifluoroacetate salt

Prepared from 4-chloroaniline.

^{1}H NMR (d_4 MeOH): 7.97 ppm (2 H, m, Ar); 7.70 - 7.50 (13 H, m, Ar); 5.80 (1 H, s, C<u>H</u>Ph); 4.21 (2 H, s, C<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 3.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 394 $(MH)^+$.

Example 20

1-[3-(Aminomethyl)benzoyl-D-phenylglycinyl]piperidine trifluoroacetate salt

Prepared from piperidine.

^{1}H NMR (d_4 MeOH): 7.97 ppm (2 H, m Ar); 7.65 - 7.30 (7 H, m, Ar); 6.10 (1 H, s, C<u>H</u>Ph); 4.21 (2H, s, C<u>H</u>$_2$NH$_2$); 3.79 (1H, m, pip); 3.50 (3H, m, pip); 1.70 - 1.21 (5 H, m, pip).

HPLC (Luna 2, Gradient 1): rt = 3.36 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 394 $(MH)^+$.

Example 21

1-[3-(Aminomethyl)benzoyl-D-phenylglycinyl]-3-[(*N*-ethyl-*N*-methyl)amido]piperidine trifluoroacetate salt

Prepared from 3-[(*N*-ethyl-*N*-methyl)amidocarbonyl]-piperidine.

^{1}H NMR (CD_3CN): The compound contains two chiral centres and is therefore a mixture of diastereomers, as well as exhibiting rotamers due to the *N*-ethyl-*N*-methyl amide. 8.45 - 7.78 ppm (5 H, m, Ar and NH); 7.72 - 7.28 (5 H, m, Ph); 6.10 - 5.90 (1 H, m, C<u>H</u>Ph); 4.61 - 4.35 (1 H, m, piperidine H); 4.14 (2 H, br s, C<u>H</u>$_2$NH$_2$); 3.97 - 3.66 (1 H, m, piperidine H); 3.50 - 2.35 (12 H, m) 1.90 - 0.75 (4 H, m).

HPLC (Luna 2, Gradient 1): rt = 3.13 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 437 $(MH)^+$.

Example 22

1-[3-(Aminomethyl)benzoyl-D-phenylglycinyl] pyrrolidine trifluoroacetate salt

Prepared from pyrrolidine.

^{1}H NMR (d_4 MeOH): 7.95 ppm (2 H, m, Ar); 7.72-7.34 (7 H, m, Ar); 5.91 (1 H, m, C<u>H</u>Ph); 4.20 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.80 (2 H, m, pyr); 3.61 (2 H, m, pyr); 3.50 (2 H, m, pyr); 3.19 (2 H, m, pyr).

HPLC (Luna 2, Gradient 1): rt = 3.06 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.57 minutes, 338 $(MH)^+$.

Example 23

2-[3-(Aminomethyl)benzoyl-D-phenylglycinyl] decahydroisoquinoline trifluoroacetate salt

Prepared from decahydroisoquinoline.

^{1}H NMR (d_4 MeOH): 7.70 ppm (2 H, br s, Ar); 7.41 -7.09 (7 H, m, Ar); 5.95-5.78 (1H, m, C<u>H</u>Ph); 3.95 (2H, s, C<u>H</u>$_2$NH$_2$); 1.7 - 0.65 (16 H, m, decahydroisoquinoline C(H)'s).

HPLC (Luna 2, Gradient 1): rt = 4.11 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 406 $(MH)^+$.

Example 24

3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared from 2,3-dihydro-6-nitroindole.

^{1}H NMR (d_4 MeOH): 7.91 ppm (2 H, m, Ar); 7.75 (1 H, s, Ar); 7.57 (4 H, m, Ar); 7.34 (5 H, m, Ar); 5.75 (1 H, s, C<u>H</u>Ph); 4.15 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.75 (2 H, t, J = 7.5 Hz, dihydroindole C(2)H$_2$); 3.20 (2 H, t, J = 7.5 Hz, dihydroindole C(3)H$_2$).

HPLC (Luna 2, Gradient 1): rt = 2.54 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.24 minutes, 401 $(MH)^+$.

Example 25

3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindolamide trifluoroacetate salt

Prepared from 2,3-dihydroindole.

^{1}H NMR (d_4 MeOH): 8.92 ppm (1 H, d, J = 7 Hz, NH); 8.22 (1 H, d, J = 9.5 Hz, dihydroindole C(7)H); 7.97 (2 H, m, Ar); 7.48 (3 H, m, Ar); 7.19 (2 H, m, Ar); 7.08 (1 H, m, Ar); 6.02 (1 H, m, C<u>H</u>Ph); 4.41 (1 H, m, dihydroindole C(2)H); 4.19 (2H, s, C<u>H</u>$_2$NH$_2$); 3.78 (1H, m, dihydroindole C(2)H); 3.23 (1H, m, dihydroindole C(3)H); 3.07 (1H, m, dihydroindole C(3)H).

HPLC (Luna 2, Gradient 1): rt = 3.79 minutes.

LC/MS (Luna 2, gradient 4): rt = 2.21minutes, 386 (MH)$^+$.

Example 26

3-(Aminomethyl)benzoyl-D-phenylglycine 1-methyl-2,3-dihydro-indol-6-amide bis(trifluoracetate salt)

Prepared from 6-amino-2,3-dihydro-1-methylindole.

^{1}H NMR (d_4 MeOH): 8.0 ppm (2 H, m, Ar); 7.65 (4 H, m, Ar); 7.40 (3 H, m, Ar); 7.15 (2 H, m, Ar); 6.95 (1 H, m, Ar); 5.83 (1 H, s, C<u>H</u>Ph); 4.20 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.42 (2 H, m, dihydroindole C(2)H); 2.98 (2H, m, dihydroindole C(3)H); 2.82 (3H, s, NCH$_3$).

HPLC (Luna 2, Gradient 1): rt = 2.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.88 minutes, 415 (MH)$^+$.

Example 27

3-(Aminomethyl)benzoyl-D-phenylglycine 3-acetylamino-4-methylphenylamide trifluoroacetate salt

Prepared from 2-methyl-5-nitroacetanilide.

^{1}H NMR (D_2O): 7.78 - 7.19 (12 H, m, Ar), 5.64 (1H, s, α-C<u>H</u>),

4.17 (2 H, s, CH_2NH_2), 2.12 (6H, s, 2 x CH_3)
HPLC (Luna 2, Gradient 1): rt = 3.10 minutes.
LC/MS (Luna 2, Gradient 4):rt = 1.56 minutes, 431 (MH^+).

Example 28

3-(Aminomethyl)benzoyl-D-phenylglycine (*R/S*)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamide trifluoroacetate salt

Prepared from (*R/S*)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine, synthesised as described below.

(*R/S*)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine

A suspension of methyltriphenylphosphonium iodide (680 mg, 1.68 mmol) in tetrahydrofuran (7 mL) was cooled to -45°C. n-Butyllithium (1.0 mL, 1.6 M in hexane, 1.60 mmol) was then added dropwise, and the solution was stirred for 1 hour. 1,2,3,4-Tetrahydro-7-nitro-1-oxonaphthalene (200 mg, 1.05 mmol) in tetrahydrofuran (3 mL) was then added over 5 minutes. The reaction mixture was allowed to warm to room temperature before being quenched with water (20 mL). The solution was then extracted with dichloromethane (2 x 25 mL), the solvent was dried ($MgSO_4$) and concentrated under reduced pressure to give a black oil. The crude product was then purified by flash chromatography (ethyl acetate / hexane; 1:40) to afford 5,6,7,8-tetrahydro-8-methylene-2-nitro-naphthalene as a white solid (150 mg, 76%).
A solution of the olefin (100 mg, 0.53 mmol) in methanol (2 mL) was stirred over 10% palladium on carbon (20 mg). The mixture was purged with hydrogen and stirred for 18 hrs under a balloon of hydrogen. The reaction mixture was then filtered through celite, washing with additional methanol,

and concentrated under reduced pressure to afford (R/S)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine as a colourless oil (75 mg, 82%).

^{1}H NMR ($CDCl_3$): 7.53 ppm (1 H, d, *J* = 8 Hz, C(4)H); 7.21 (1 H, d, *J* = 2 Hz, C(1)H); 7.18 (1 H, dd, *J* = 8, 2 Hz, C(3)H); 4.16 (2 H, br s, NH_2); 3.52 (1 H, sextet, *J* = 7 Hz, C<u>H</u>CH_3); 3.41-3.25 (2 H, m, C(5)H_2); 2.61-2.45 (2 H, m, tetrahydronaphthalene C(6)H and/or C(7)H); 2.43-2.32 (1 H, m, tetrahydronaphthalene C(6) or C(7)H); 2.23-2.12 (1 H, m, tetrahydronaphthalene C(6)H or C(7)H); 1.96 (3 H, d, *J* = 7 Hz, CH_3).

3-(Aminomethyl)benzoyl-D-phenylglycine (*R/S*)-8-methyl-5,6,7,8-tetrahydro-naphth-2-ylamide trifluoroacetate salt.

^{1}H NMR (MeOH): 7.95 ppm (2 H, br s, Ar); 7.76 - 7.60 (4 H, m, Ar); 7.48 - 7.31 (4 H, m, Ar); 7.29 - 7.21 (1 H, m, Ar); 6.97 (1 H, d, *J* = 8 Hz, Ar); 5.80 (1 H, s, C<u>H</u>Ph); 4.18 (2 H, s, C<u>H</u>$_2$$NH_2$); 2.90 - 2.69 (3 H, m, tetrahydronaphthalene C(5)H and C(8)H_2); 1.99-1.80 (2 H, m, tetrahydronaphthalene C(6)H and/or C(7)H); 1.75 - 1.63 (1 H, m, tetrahydronaphthalene C(6) or C(7)H); 1.58 - 1.40 (1 H, m, tetrahydro-naphthalene C(6)H or C(7)H); 1.27 (3 H, d, *J* = 7 Hz, CH_3).

HPLC (Symmetry, Gradient 2): rt = 6.73 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.53 minutes, 428 $(MH)^+$.

Example 29

3-(Aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide trifluoroacetate salt

Prepared from 5-aminoindane.

^{1}H NMR (d_4 MeOH): 8.16 ppm (1 H, s, 3-(aminomethyl)benzoyl

C(2)H); 8.15 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.96 - 7.54 (8 H, m, Ar); 7.45 (1 H, d, J = 8 Hz, indane C(6)H or C(7)H); 7.33 (1 H, d, J = 8 Hz, indane C(6)H or C(7)H); 6.0 (1 H, s, C<u>H</u>Ph); 4.39 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.06 (4 H, q, J = 7 Hz, indane C(1)H$_2$ and C(3)H$_2$); 2.26 (2 H, quintet, J = 7 Hz, indane C(2)H$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.02 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.42 minutes, 400 $(MH)^+$.

Example 30

3-(Aminomethyl)benzoyl-D-phenylglycine 4-isopropylphenylamide trifluoroacetate salt

Prepared from 4-isopropylaniline.

^{1}H NMR (d$_4$ MeOH): 8.17 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.15 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.83 - 7.59 (9 H, m, Ar); 7.38 (2 H, d, J = 8.5 Hz, Ar); 6.0 (1 H, s, C<u>H</u>Ph); 4.38 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.09 (1 H, septet, J = 7 Hz, C<u>H</u>(CH$_3$)$_2$); 1.42 (6 H, d, J = 7 Hz, CH(C<u>H</u>$_3$)$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.21 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.48 minutes, 402 $(MH)^+$.

Example 31

3-(Aminomethyl)benzoyl-D-phenylglycine (*1S,2S,3S,5R*)-isopinocamphamide trifluoroacetate salt

Prepared from (*1S,2S,3S,5R*)-(+)-isopinocampheylamine.

^{1}H NMR (d$_4$ MeOH): 7.96 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.95 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.67 - 7.25 (7 H, m, Ar); 5.70 (1 H, s, C<u>H</u>Ph); 4.28 (1 H, m, isopinocampheyl C(1)H); 4.20 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.55 - 1.77 (5 H, m, isopinocampheyl H's); 1.26 (3 H, s, CH$_3$); 1.14 (3 H,

d, J = 7Hz, isopinocampheyl C(10)H_3); 1.08 (3 H, s, CH_3); 1.04 - 0.94 (2 H, m, isopinocampheyl H's).

HPLC (Luna 2, Gradient 1): rt = 4.34 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.34 minutes, 420 $(MH)^+$.

Example 32

3-(Aminomethyl)benzoyl-D-phenylglycine 4-(1-hydroxyethyl)phenylamide trifluoroacetate salt

Prepared from 1-(4-aminophenyl)ethanol.

^1H NMR (d_4 MeOH): 7.85 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.84 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.56 - 7.05 (11 H, m, Ar); 5.72 (1 H, s, C<u>H</u>Ph); 4.69 (1 H, q, J = 6.5 Hz, C<u>H</u>(OH)CH_3); 4.08 (2 H, s, $C\underline{H}_2NH_2$); 1.31 (3 H, d, J = 6.5 Hz, CH_3).

HPLC (Luna 2, Gradient 1): rt = 3.0 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 404 $(MH)^+$.

Example 33

3-(Aminomethyl)benzoyl-D-phenylglycine *cis*-2-aminocyclohexyl-amide bis(trifluoroacetate) salt

Prepared from *cis*-1,2-diaminocyclohexane.

^1H NMR (d_4 MeOH): 8.08 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.06 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.79 - 7.48 (7 H, m, Ar); 5.87 (1 H, s, C<u>H</u>Ph); 4.46 (1 H, m, cyclohexyl C(1)H); 4.30 (2 H, s, $C\underline{H}_2NH_2$); 3.54 (1 H, m, cyclohexyl C(2)H); 2.11 - 1.52 (8 H, m, cyclohexyl H's).

HPLC (Luna 2, Gradient 1); rt = 2.40 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.08 minutes, 381 $(MH)^+$.

Example 34

1-[3-(Aminomethyl)benzoyl-D-phenylglycinyl] 4-hydroxypiperidine hydrochloride salt

Prepared from 4-hydroxypiperidine.

^{1}H NMR (d_4 MeOH): 7.84 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.80 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.59 - 7.17 (7 H, m, Ar); 6.03 (1 H, s, C**H**Ph); 4.11 (2 H, s, CH_2NH_2); 3.90 (1 H, m, piperidyl C(4)H); 3.62 (2 H, m, piperidyl C(2)H and C(6)H); 3.14 - 2.94 (2 H, m, piperidyl C(2)H and C(6)H); 1.93 - 1.16 (4 H, m, piperidyl C(3)H_2 and C(5)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.56 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.36 minutes, 368 $(MH)^+$.

Example 35

3-(Aminomethyl)benzoyl-D-phenylglycine 1-acetyl-2,3-dihydro-indol-6-amide trifluoroacetate salt

1-Benzyloxycarbonyl-2,3-dihydro-6-nitroindole

A solution of 6-nitroindoline (10.0 g, 0.061 mol), triethylamine (22.7 mL, 0.16 mol) and dimethylaminopyridine (50 mg, cat.) in dichloromethane (130 mL) was stirred at 0°C and benzyl chloroformate (18 mL, 0.12 mol) was added slowly. The mixture was allowed to warm to room temperature overnight. The mixture was washed with water (50 mL), 5% aqueous HCl (100 mL), saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The dichloromethane was dried ($MgSO_4$) and evaporated under reduced pressure to give an orange solid. This was triturated in diethyl ether (150 ml) to give a yellow solid (12.34 g, 68%).

^{1}H NMR ($CDCl_3$): 7.80 ppm (1 H, dd, J = 8, 2 Hz, C(7)H); 7.35

(5 H, m, Ph); 7.20 (2 H, m, C(4)H and C(5)H); 5.25 (2 H, br s, CH_2Ph); 4.11 (2 H, t, *J* = 8 Hz, dihydroindole C(2)H_2); 3.15 (2 H, t, *J* = 8 Hz, dihydroindole C(3)H_2).

6-amino-1-benzyloxycarbonyl-2,3-dihydroindole

A mixture of 1-benzyloxycarbonyl-2,3-dihydro-6-nitroindole (1.0 g, 3.36 mmol) and tin(II) chloride dihydrate (3.78 g, 16.75 mmol) in ethanol (70 mL) was heated at 70°C, under an atmosphere of nitrogen, for 3 hours. The solution was cooled and the solvent evaporated under reduced pressure to give an off-white solid. The solid was partitioned between water (50 mL) and ethyl actate (100 mL) and the aqueous layer basified (pH 11) with 1M sodium hydroxide solution. The mixture was filtered to remove tin salts and the ethyl acetate was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the amine as a yellow oil (0.89 g, 99 %) ^{1}H NMR ($CDCl_3$): 7.51 - 7.33 ppm (6 H, m, Ph + C(7)H); 6.93 (1 H, d, *J* = 8 Hz, C(4)H); 6.32 (1 H, dd, J = 8, 2 Hz, C(5)H); 5.28 (2 H, br s, CH_2Ph); 4.01 (2 H, t, *J* = 7.5 Hz, dihydroindole C(2)H_2); 3.66 (2 H, bs, NH_2); 3.05 (2 H, t, *J* = 7.5 Hz, dihydroindole C(3)H_2).

***N*-BOC-D-phenylglycine 1-benzyloxycarbonyl-2,3-dihydroindol-6-amide**

A solution of *N*-BOC-D-phenylglycine (0.83 g, 3.28 mmol), 1-[3-(dimethyl-amino)propyl]-3-ethylcarbodiimide hydrochloride (0.75 g, 3.9 mmol), 1-hydroxy-7-azabenzotriazole (0.54 g, 3.9 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg, cat.) in dimethylformamide (20 mL) was stirred at room temperature and a solution of the above amine (0.88 g, 3.28 mmol) in

dimethylformamide (20 mL) was added and the mixture allowed to stir overnight. The dimethylformamide was evaporated under reduced pressure and the resulting oil partitioned between water (50 mL) and ethyl acetate (50 mL). The ethyl acetate was washed with 5% aqueous HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the amide as a golden foam (1.6 g, 97 %).

^1H NMR ($CDCl_3$): 7.43 - 7.10 ppm (13 H, m, Ar): 6.85 (1 H, d, J = 6 Hz, NH); 5.61 (1 H, br s, NH); 5.03 (2 H, br s, CH_2Ph); 3.85 (2 H, t, J = 7 Hz, dihydroindole C(2)H_2); 2.85 (2 H, t, J = 8 Hz, dihydroindole C(3)H_2); 1.19 (9 H, s, ^tBu).

D-phenylglycine 1-benzyloxycarbonyl-2,3-dihydroindol-6-amide trifluoroacetate salt

Trifluoroacetic acid (5 mL) was added to a solution of the above foam in dichloromethane (20 mL) and the solution was allowed to stir for 2 hours at room temperature. The solvent was evaporated under reduced pressure to give the amine trifluoracetate salt as a red foam (1.5 g, 91 %) which was used without further purification.

3-(*N*-BOC-Aminomethyl)benzoyl-D-phenylglycine (1-benzyloxycarbonyl-2,3-dihydro)-indol-6-amide

A solution of 3-(*N*-BOC-aminomethyl)benzoic acid (0.798 g, 3.2 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.73 g, 3.8 mmol), 1-hydroxy-7-azabenzotriazole (0.52 g, 3.8 mmol) and triethylamine (1.0 mL, 7.2 mmol) in dimethylformamide (10 mL) was stirred at room temperature and a solution of the above amine (1.5 g,

3.0 mmol) in dimethylformamide (5 mL) was added. The mixture was stirred overnight before the dimethylformamide was evaporated under reduced pressure, and the resulting oil partitioned between water (50 mL) and ethyl acetate (50 mL). The ethyl acetate layer was washed with 5% aqueous HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow solid. ^1H NMR ($CDCl_3$): 7.75 - 7.22 ppm (17 H, m, Ar): 7.05 (1 H, d, J = 5.5 Hz, NH); 5.74 (1H, d, J = 6 Hz, CHPh); 5.21 (2 H, s, OCH_2Ph); 4.89 (1 H, br s, NH); 4.32 (2 H, d, J = 6 Hz, CH_2NHBOC); 4.02 (2H, t, J = 8 Hz, dihydroindole C(2)H_2); 3.05 (2H, t, J = 8 Hz, dihydroindole C(3)H_2); 1.4 (9 H. s, ^{t}Bu).

3-(*N*-BOC-Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol-6-amide

A solution of the above solid in methanol (50 mL) was stirred over 10%Pd/C (500 mg) under an atmosphere of H_2 and heated under reflux for 2 hours. The mixture was cooled, filtered and the solvent evaporated under reduced pressure to provide the unprotected dihydroindole as a yellow foam (1.4g, 88%) which was used without further purification.

3-(Aminomethyl)benzoyl-D-phenylglycine 1-acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt

A solution of the dihydroindole (500 mg, 1.0 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (20 mL) was stirred at 0°C and acetyl chloride (86 mg, 1.1 mmol) was added dropwise, then left to stir overnight. The mixture was washed with 5% aqueous HCl (10 mL) and the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by

flash column chromatography (ethyl acetate / hexane, 1:1) to give a yellow oil. The oil was dissolved in dichloromethane (20 mL) and treated with trifluoroacetic aid (5 mL). After stirring for 2 hours the solvent was evaporated under redued pressure to an oil, which after triturating with diethyl ether gave the amine as its trifluoroacetate salt as a white solid (337 mg, 61 %).

^{1}H NMR (d_4 MeOH): 8.30 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.60 (4 H, m, Ar); 7.39 (4 H, 3, m, Ar); 7.22 (1 H, d, J = 10 Hz, Ar); 5.82 (1 H, s, C<u>H</u>Ph); 4.2 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.15 (2 H, t, J = 7 Hz, dihydroindole C(2)H$_2$); 3.17 (2 H, t, J = 7 Hz, dihydroindole C(3)H$_2$); 2.25 (3 H, s, CH$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.39 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 443 $(MH)^+$.

Examples 36 - 60 were prepared from the intermediate 3-(*N*-BOC-aminomethyl)-benzoyl-D-phenylglycine 2,3-dihydroindol-5-amide, described for Example 29, and the appropriate carboxylic acid or derivative, using standard chemical methods and protecting other functionality where required.

Example 36

3-(Aminomethyl)benzoyl-D-phenylglycine 1-propanoyl-2,3-dihydro-indol-6-amide trifluoroacetate salt

Prepared using propanoyl chloride.

^{1}H NMR (d_4 MeOH): 8.58 ppm (1 H, d, J = 1.2 Hz, dihydroindole C(7)H); 8.18 (2 H, m, Ar); 7.82 (4 H, m, Ar); 7.59 (4 H, m, Ar); 7.37 (1 H, m, Ar); 6.03 (1 H, s, C<u>H</u>Ph); 4.39 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.31 (2 H, t, J = 9 Hz, dihydroindole C(2)H); 3.37 (2 H, t, J = 9 Hz, dihydroindole C(3)H); 2.73

(2 H, q, J = 7.5 Hz, CH_2CH_3); 1.47 (3 H, t, J = 7.5 Hz, CH_2CH_3).

HPLC (Luna 2, Gradient 1): rt = 3.55 minutes.

LC/MS (Luna 2, Gradient 4):rt = 1.94 minutes, 457 $(MH)^+$.

Example 37

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-methyl-propanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using 2-methylpropanoyl chloride.

^1H NMR (d_4 MeOH): 8.32 ppm (1 H, s, dihydroindole C(7)H); 7.98 (2 H, m, Ar); 7.60 (4 H, m, Ar); 7.43 (4 H, m, Ar); 7.18 (1 H, m, Ar); 5.83 (1 H, s, CHPh); 4.21 (4 H, m, CH_2NH_2 and dihydroindole C(2)H); 3.18 (2 H, t, J = 9 Hz, dihydroindole C(3)H), 2.95 (1 H, m, $CH(CH_3)_2$); 1.22 (6 H, d, J = 8 Hz, $CH(CH_3)_2$).

HPLC (Luna 2, Gradient 1): rt = 3.74 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 471 $(MH)^+$.

Example 38

3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-alaninoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using D-alanine.

^1H NMR (d_4 MeOH): 8.40 ppm (1 H, s, Ar); 8.01 (2 H, m, Ar); 7.65 (4 H, m, Ar); 7.45 (4 H, m, Ar); 7.25 (1 H, d, J = 10 Hz, Ar); 5.85 (1 H, s, CHPh); 4.4 (1 H, q, J = 7 Hz, alaninyl $CHNH_2$); 4.25 (2 H, s, $ArCH_2NH_2$); 4.25 (2 H, t, J = 8 Hz, dihydroindole $C(2)H_2$); 3.28 (2 H, t, J = 8 Hz, dihydroindole $C(3)H_2$); 1.65 (3 H, d, J = 7 Hz, CH_3).

HPLC (Luna 2, Gradient 1): rt = 2.85 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 472 $(MH)^+$.

Example 39

3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-alaninoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using L-alanine.

^1H NMR (d_4 MeOH): 8.43 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.63 (4 H, m, Ar); 7.45 (4 H, m, Ar); 7.25 (1 H, d, J = 10 Hz, Ar); 5.85 (1 H, s, C<u>H</u>Ph); 4.35 (1 H, q, J = 7 Hz, alaninyl C<u>H</u>NH_2); 4.25 (2H, t, J = 7.5 Hz, indoline C(2)H_2); 4.2 (2 H, s, $C\underline{H}_2NH_2$); 3.25 (2H, t, J = 8 Hz, indoline C(3)H_2); 1.6 (3 H, d, J = 7 Hz, $C\underline{H}_3$).

HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 472 $(MH)^+$.

Example 40

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(*N*-acetyl-D-alaninoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using *N*-acetyl-D-alanine.

^1H NMR (d_4 MeOH): 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.61 (4 H, m, Ar); 7.40 (4 H, m, Ar); 7.18 (1 H, d, J = 9 Hz, Ar); 5.83 (1 H, s, C<u>H</u>Ph); 4.70 (1 H, br m, C<u>H</u>NHAc); 4.38 (1 H, m, indoline C(2)H); 4.21 (2H, s, $C\underline{H}_2NH_2$); 4.20 (1 H, t, J = 8 Hz indoline C(2)H); 3.2 (2 H, t, J = 8 Hz, indoline C(3)H_2); 2.01 (3 H, s, $COC\underline{H}_3$); 1.4 (3 H, d, J = 7 Hz, CH_3).

HPLC (Luna 2, Gradient 1): rt = 3.24 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 514 $(MH)^+$.

Example 41

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(*N*-acetyl-L-alaninoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using *N*-acetyl-L-alanine.

^{1}H NMR (d_4 MeOH): 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.62 (4 H, m, Ar); 7.38 (4 H, m, Ar); 7.18 (1 H, d, Ar); 5.83 (1 H, s, C<u>H</u>Ph); 4.70 (1 H, m, C<u>H</u>NHAc); 4.35 (1 H, m, dihydroindole C(2)H); 4.2 (2H, s, C<u>H</u>$_2$NH$_2$); 4.2 (1H, m, dihydroindole C(2)H); 3.2 (2 H, t, J = 8 Hz, dihydroindole C(3)H$_2$); 2.0 (3 H, s, COCH$_3$); 1.4 (3 H, d, J = 7 Hz, CH$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.19 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.67 minutes, 514 $(MH)^+$.

Example 42

3-(Aminomethyl)benzoyl-D-phenylglycine 1-aminoacetyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using glycine.

^{1}H NMR (d_4 MeOH): 8.41 (1 H, s, dihydroindole C(7)H); 7.97 (2 H, br s, Ar); 7.58 (4 H, m, Ar); 7.22 (1 H, d, J = 8 Hz, Ar); 5.84 (1 H, s, C<u>H</u>Ph); 4.20 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.15 (2 H, t, J = 9 Hz, dihydroindole C(2)H); 4.04 (2 H, s, COC<u>H</u>$_2$NH$_2$); 3.23 (2H, t, J = 9 Hz, dihydroindole C(3)H).

HPLC (Luna 2, Gradient 1): rt = 2.77 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.24 minutes, 458 $(MH)^+$.

Example 43

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-methylbutanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using 3-methylbutanoyl chloride.

^{1}H NMR (d_4 MeOH): 8.40 ppm (1 H, s, Ar); 8.02 (2 H, m, Ar); 7.67 (4 H, m, Ar); 7.22 (1 H, d, J = 11 Hz, Ar); 5.90 (1 H, s, C<u>H</u>Ph); 4.27 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.22 (2 H, t, J = 8 Hz, indoline C(2)H$_2$); 3.22 (2H, t, J = 8 Hz, indoline C(3)H$_2$); 2.45 (2 H, d, J = 7 Hz, COC<u>H</u>$_2$); 2.28 (1 H, septet, J = 7 Hz, C<u>H</u>Me$_2$); 1.1 (6 H, d, J = 7 Hz, CH(C<u>H</u>$_3$)$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.18 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 485 $(MH)^+$.

Example 44

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(benzyloxy)-acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using 2-benzyloxyacetyl chloride.

^{1}H NMR (d_4 MeOH): 8.40 ppm (1 H, s, Ar); 8.02 (2 H, m, Ar); 7.65 (5 H, m, Ar); 7.45 (10 H, m, Ar); 7.22 (1 H, d, J = 10 Hz, Ar); 5.91 (1 H, s, C<u>H</u>Ph); 4.73 (2 H, s, COCH); 4.35 (1 H, q, C<u>H</u>NH$_2$); 4.37 (2 H, s, C<u>H</u>$_2$Ph); 4.25 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.12 (2 H, t, J = 7.5 Hz, indoline C(2)H$_2$); 3.2 (2 H, t, J = 7.5 Hz, indoline C(3)H$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.25 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 549 $(MH)^+$.

Example 45

3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-threoninoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using L-threonine.

^{1}H NMR (d_4 MeOH): 8.31 ppm (1 H, s, Ar); 7.80 (2 H, m, Ar); 7.45 (4 H, m, Ar); 7.25 (4 H, m, Ar); 7.05 (1 H, d, Ar); 5.65 (1 H, s, C<u>H</u>Ph); 4.10 (2 H, t, J = 8 Hz, indoline C(2)H$_2$); 4.02 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.11 (2 H, t, J = 8 Hz,

indoline C(3)H_2); 1.21 (3H, d, CH_3); other signals obscured by solvent.

HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.65 minutes, 502 $(MH)^+$.

Example 46

3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-prolinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using L-proline.

^1H NMR (d_4 MeOH): 8.47 ppm (1 H, s, Ar); 8.05 (2 H, m, Ar); 7.75 - 7.65 (4 H, m, Ar); 7.56 - 7.47 (4 H, m, Ar); 7.30 (1 H, d, J = 9 Hz, Ar); 5.91 (1 H, s, C<u>H</u>Ph); 4.73 (1 H, t, J = 6.5 Hz, proline C(2)H); 4.25 (4 H, m, CH_2NH_2 and indoline C(2)H_2); 3.65-3.32 (3 H, m, indoline C(3)H_2 and proline C(5)H); 2.70 (1 H, m, proline C(5)H); 2.33 - 2.15 (4 H, m, proline C(3)H_2 and C(4)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 498 $(MH)^+$.

Example 47

3-(Aminomethyl)benzoyl-D-phenylglycine 1-((*S*)-2-hydroxypropanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using (*S*)-2-hydroxypropanoic acid.

^1H NMR (d_4 MeOH): 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.66 - 7.56 (4 H, m, Ar); 7.45 - 7.37 (4 H, m, Ar); 7.18 (1 H, d, J = 9 Hz, Ar); 5.83 (1 H, s, C<u>H</u>Ph); 4.58 (1H, m, C<u>H</u>OH); 4.31 (1H, m, indoline C(2)H); 4.21 (2 H, s, $C\underline{H}_2NH_2$); 4.15 (1 H, m, indoline C(2)H); 3.18 (2 H, t, J = 8 Hz, indoline C(3)H_2); 1.4 (3 H, d, J = 7 Hz, CH_3).

HPLC (Luna 2, Gradient 1): rt = 3.31 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 473 $(MH)^+$.

Example 48

3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-prolinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using D-proline.

^1H NMR (d_4 MeOH): 8.41 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.48 - 7.39 (4 H, m, Ar); 7.23 (1 H, d, J = 11 Hz, Ar); 5.82 (1 H, s, C<u>H</u>Ph); 4.63 (1 H, m, proline C(2)H); 4.24 (4 H, m, CH_2NH_2 and indoline C(2)H_2); 3.52-3.24 (3 H, m, indoline C(3)H_2 and proline C(5)H); 2.63 (1 H, m, proline C(5)H); 2.23 - 2.08 (4 H, m, proline C(3)H_2 and C(4)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.

HPLC (Symmetry, Gradient 2): rt = 4.87 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 498 $(MH)^+$.

Example 49

3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-serinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using L-serine.

^1H NMR (d_4 MeOH): 8.40 ppm (1 H, s, Ar); 7.95 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.47 - 7.39 (4 H, m, Ar); 7.23 (1 H, d, J = 10 Hz, Ar); 5.81 (1 H, s, C<u>H</u>Ph); 4.4 (1 H, dd, J = 12 Hz, 4 Hz, serine CH_aH_bOH); 4.25 (2 H, t, J = 7 Hz, indoline C(2)H_2); 4.20 (2 H, s, $C\underline{H}_2NH_2$); 4.05 (1 H, dd, J = 12, 6 Hz, serine $CH_a\underline{H}_bOH$); 3.91 (1 H, m, serine $C\underline{H}NH_2$); 3.25 (2 H, t, J = 7 Hz, indoline C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 488 $(MH)^+$.

Example 50

3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-serinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using D-serine.

^1H NMR (d_4 MeOH): 8.42 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.47 - 7.39 (4 H, m, Ar); 7.23 (1H, d, J = 9 Hz, Ar); 5.82 (1 H, s, C<u>H</u>Ph); 4.41 (1 H, dd, J = 12, 4 Hz, serine C<u>H</u>$_a$H$_b$OH); 4.25 (2 H, t, J = 7.5 Hz, indoline C(2)H_2); 4.2 (2 H, s, C<u>H</u>$_2$NH$_2$); 4.05 (1 H, dd, J = 12, 6 Hz, serine CH$_a$<u>H</u>$_b$OH); 3.9 (1 H, mserine C<u>H</u>NH$_2$); 3.25 (2 H, t, J = 7.5 Hz, indoline C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.78 minutes.

HPLC (Symmetry, Gradient 2): rt = 4.61 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.65 minutes, 488 $(MH)^+$.

Example 51

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-pyridyl-acetyl)-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using 3-pyridylacetic acid.

^1H NMR (d_3 acetonitrile): 8.91 ppm (1 H, br s, Ar), 8.73-8.55 (2 H, m, Ar), 8.35 (1 H, br s, Ar), 8.15 (1 H, d, J = 10 Hz, Ar), 8.05-7.95 (2 H, m, Ar), 7.80 (1H, d, J = 10 Hz, Ar), 7.74 - 7.15 (10 H, m, Ar & 2 x amide N<u>H</u>), 5.69 (1 H, d, J = 7 Hz, C<u>HPh</u>), 4.25 - 4.12 (4 H, m, ArC<u>H</u>$_2$N & dihydroindole C(2)H_2), 3.98 (2 H, s, C(O)C<u>H</u>$_2$Py), 3.17 (2 H, t, J = 8 Hz, dihydroindole C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.96 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 520 (MH^+).

Example 52

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(*N*-acetyl)-aminoacetyl-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using *N*-acetylglycine.

^1H NMR (d_4 MeOH): 8.31 ppm (1 H, s, Ar); 7.95 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.43 - 7.38 (4 H, m, Ar); 7.18 (1H, d, J = 10 Hz, Ar); 5.81 (1H, s, C<u>H</u>Ph); 4.23 - 4.11 (6 H, m, $ArCH_2NH_2$, aminoacetyl CH_2 and dihydroindole C(2)H_2); 3.21 (2 H, t, J = 7 Hz, dihydroindole C(3)H_2); 2.07 (3H, s, $COCH_3$).

HPLC (Luna 2, Gradient 1): rt = 3.33 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.20 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 500 $(MH)^+$.

Example 53

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(hydroxyacetyl)-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using 2-benzyloxyacetic acid.

^1H NMR (d_4 MeOH): 8.25 ppm (1 H, s, Ar); 7.85 (2 H, m, Ar); 7.54 - 7.47 (4 H, m, Ar); 7.35 - 7.26 (4 H, m, Ar); 7.10 (1 H, d, J = 11 Hz, Ar); 4.21 (2 H, s, C<u>H</u>$_2$OH); 4.10 (2 H, s, C<u>H</u>$_2$$NH_2$); 3.95 (2 H, t, J = 7.5 Hz, dihydroindole C(2)H_2); 3.21 (2 H, t, J = 7.5 Hz, dihydroindole C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 3.23 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.26 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.67 minutes, 500 $(MH)^+$.

Example 54

3-(Aminomethyl)benzoyl-D-phenylglycine 1-phenylacetyl-2,3-dihydroindol-6-amide trifluoroacetate salt

Prepared using phenylacetic acid.

^{1}H NMR (d_3 acetonitrile): 8.78 (1 H, br s, Ar), 8.23 (1 H, br s, Ar), 7.90 (2 H, s, Ar), 7.73 (1H, d, J = 10 Hz, Ar), 7.60 - 7.01 (14 H, m, Ar & 2 x amide NH), 5.60 (1 H, d, J = 7 Hz, CHPh), 4.10 - 3.97 (4 H, m, $ArCH_2N$ & dihydroindole C(2)H_2), 3.71 (2 H, s, $PhCH_2$), 2.99 (2 H, t, J = 8 Hz, dihydroindole C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 4.17 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.26 minutes, 519 (MH^+).

Example 55

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(methylamino)-acetyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using sarcosine.

^{1}H NMR (d_4 MeOH): 8.39 ppm (1 H, s, indoline C(7)H); 7.95 (2 H, br s, 3-(aminomethyl)phenyl C(2)H and C(6)H); 7.72 - 7.53 (4 H, m, Ar); 7.47 - 7.31 (4 H, m, Ar); 7.24 (1 H, d, J = 10 Hz, indoline C(4)H or C(5)H); 5.82 (1 H, br s, CHPh); 4.20 (2 H, s, CH_2NH_2 or C(O)CH_2NHMe); 4.15 (2 H, s, CH_2NH_2 or C(O)CH_2NHMe); 4.10 (2 H, t, J = 9 Hz, indoline C(2)H_2); 3.25 (2 H, t, J = 9 Hz, indoline C(3)H_2); 2.81 (3 H, s, CH_3).

HPLC (Symmetry C8, Gradient 2): rt = 4.75 min.

LCMS (Luna 2, Gradient 4): rt = 1.45 min, 472 $(MH)^+$.

Example 56

3-(Aminomethyl)benzoyl-D-phenylglycine 3-aminopropionyl-2,3-dihydroindol-6-amide bis(trifluoracetate) salt

Prepared using β-alanine.

^{1}H NMR (D_2O): 7.98 ppm (1 H, s, indoline C(7)H); 7.72 (2 H, br s, 3-(aminomethyl)phenyl C(2)H and C(6)H); 7.60 - 7.30 (7 H, m, Ar); 7.08 (1 H, d, J = 10 Hz, indoline C(4)H or C(5)H); 6.95 (1 H, d, J = 10 Hz, indoline C(4)H or C(5)H); 5.57 (1 H, s, C<u>H</u>Ph); 4.09 (2 H, s, Ar<u>CH$_2$</u>NH$_2$); 3.82 (2 H, t, J = 7 Hz, indoline C(3)H$_2$); 3.20 (2 H, t, J = 4.5 Hz, C(O)<u>CH$_2$</u>CH$_2$NH$_2$); 2.95 (2 H, t, J = 7 Hz, indoline C(3)H$_2$); 2.71 (2 H, t, J = 4.5 Hz, C(O)CH$_2$<u>CH$_2$</u>NH$_2$).

HPLC (Symmetry C8, Gradient 2): rt = 4.80 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.53 minutes, 472 $(MH)^+$.

Example 57

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(4-pyridyl-acetyl)-2,3-dihydroindol-6-amide bis-trifluoroacetate salt

Prepared using 4-pyridylacetic acid.

^{1}H NMR (CD_3CN): 8.91 (1 H, br s, Ar), 8.73-8.55 (2 H, m, Ar), 8.35 (1 H, br s, Ar), 8.15 (1 H, d, J = 10 Hz, Ar), 8.05-7.95 (2 H, m, Ar), 7.80 (1H, d, J = 10 Hz, Ar), 7.74 - 7.15 (10 H, m, Ar & 2 x amide N<u>H</u>), 5.69 (1 H, d, J = 7 Hz, C<u>H</u>Ph), 4.25 - 4.12 (4 H, m, PhC<u>H$_2$</u>N & dihydroindole C(2)H$_2$), 3.98 (2 H, s, C(O)C<u>H$_2$</u>Py), 3.17 (2 H, t, J = 8 Hz, dihydroindole C(3)H$_2$).

HPLC (Symmetry, Gradient 2): rt = 5.43 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.56 minutes, 520 $(MH)^+$.

Example 58

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(imidazol-4-ylacetyl)-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt

Prepared using imidazol-4-ylacetic acid.

^{1}H NMR (D_2O): 7.75 ppm (1 H, br s, NH); 7.49 (2 H, br s, Ar); 7.28 (1 H, d, *J* = 8 Hz, Ar); 7.24-7.12 (9 H, m, Ar); 6.92 (1 H, d, *J* = 8 Hz, Ar); 6.74 (1 H, d, *J* = 8 Hz, Ar); 6.28 (1H, s, NH); 5.38 (1 H, s, CHPh); 3.87 (2 H, s, $ArCH_2NH_2$); 3.72 (2 H, d, *J* 8 = Hz, dihydroindole C(2)H_2); 3.52 (2 H, br s, CH_2Im); 2.70 (2 H, t, *J* = 8 Hz, dihydroindole C(3)H_2).

HPLC (Symmetry, Gradient 2): rt = 4.89 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.45 minutes, 509 $(MH)^+$.

Example 59

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-aminothiazol-4-yl)-acetyl-2,3-dihydroindol-6-amide dihydrochloride.

Prepared using (2-formamidothiazol-4-yl)acetic acid.

^{1}H NMR (D_2O): 7.77 ppm (1 H, br s, NH); 7.51 (2 H, br s, Ar); 7.29 (1 H, d, *J* = 8 Hz, Ar); 7.24-7.03 (9 H, m, Ar); 6.91 (1 H, d, *J* = 8 Hz, Ar); 6.72 (1 H, d, *J* = 8 Hz, Ar); 6.22 (1H, s, NH); 5.32 (1 H, s, CHPh); 3.85 (2 H, s, $ArCH_2NH_2$); 3.73 (2 H, d, *J* = 8 Hz, dihydroindole C(2)H_2); 3.56 (2 H, br s, CH_2Thz); 2.76 (2 H, t, *J* = 8 Hz, dihydroindole C(3)H_2).

HPLC (Symmetry, Gradient 2): rt = 5.03 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.51 minutes, 541 $(MH)^+$.

Example 60

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-formylaminothiazol-4-yl)acetyl-2,3-dihydroindol-6-amide

trifluoroacetate salt

Prepared using (2-formylaminothiazol-4-yl)acetic acid.

^{1}H NMR (D_2O): 8.30 ppm (1 H, s, NCHO); 7.90 (1 H, br s, ArNH); 7.64 (2 H, br s, Ar); 7.42 (1 H, d, *J* = 8 Hz, Ar); 7.38 - 7.26 (9 H, m, Ar & NH); 7.01 (1 H, d, *J* = 8 Hz, Ar); 6.96 (1 H, d, *J* = 8 Hz, Ar); 6.82 (1H, s, NH); 5.50 (1 H, s, CHPh); 4.06 (2 H, s, $ArCH_2NH_2$); 3.90 (2 H, d, *J* = 8 Hz, dihydroindole C(2)H_2); 3.64 (2 H, br s, CH_2Thz); 2.90 (2 H, t, *J* = 8 Hz, dihydroindole C(3)H_2).

HPLC (Symmetry, Gradient 2): rt = 5.75 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 569 $(MH)^+$.

Example 61

3-(Aminomethyl)benzoyl-D/L-(4-aminomethyl)phenylglycine indan-5-amide bis(trifluoroacetate) salt.

Methyl 4-bromophenylacetate

Thionyl chloride (18 mL, 0.25 mol) was added dropwise to a solution of 4-bromo-phenylacetic acid (50 g; 0.23 mol) in methanol (250 mL). The resulting mixture was stirred at room temperature for 1 hour before the methanol was removed *in vacuo*. Ethyl acetate (300 mL) was added and the resulting solution was washed with water (3 x 150 mL) and 1M aqueous $NaHCO_3$ (1 x 150 mL), dried ($MgSO_4$) and evaporated to give the ester (52.8 g; 100 %) as an orange oil which was used without further purification.

^{1}H NMR ($CDCl_3$): 7.38 ppm (2 H, d, *J* = 8.4 Hz, C(2)H and C(6)H); 7.09 (2 H, d, *J* = 8.4 Hz, C(3)H and C(5)H); 3.63 (3 H, s, OMe); 3.51 (2 H, s, CH_2).

Methyl 4-cyanophenylacetate

Zinc cyanide (10.4 g, 0.088 mol) and tetrakis-(triphenylphosphine)palladium(0) (5 g, 4.4 mmol) were added to a solution of methyl 4-bromophenylacetate (20 g, 0.088 mol) in dimethylformamide (150 mL). The resulting mixture was stirred at 80°C for 5 hours, then allowed to cool to room temperature. Toluene (500 mL) and 1M aqueous ammonia (500 mL) were added, the layers were separated and the organic layer washed with brine (100 mL) and dried ($MgSO_4$). Evaporation of the solvents afforded an off-white solid, which was purified by silica gel chromatorgraphy to afford the cyano-compound as a white solid (11.3 g; 73 %).

^1H NMR ($CDCl_3$): 7.65 ppm (2 H, d, J = 8.4 Hz, C(3)H and C(5)H); 7.42(2 H, d, J = 8.1 Hz, C(2)H and C(6)H); 3.74 (3H, s, OMe); 3.72 (2H, s, CH_2).

4-Cyanophenylacetic acid

A solution of methyl 4-cyanophenylacetate (23.9 g; 0.136 mol) in ethanol (250 mL) was stirred at room temperature and a solution of sodium hydroxide (6.0 g; 0.15 mol) in water (25 mL) was added. After 2 hours the ethanol was removed *in vacuo*. Ethyl acetate (300 mL) and 5% aqueous HCl (300 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (300 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the acid (21.6 g; 99 %) which was used without further purification.

^1H NMR ($CDCl_3$): 7.57 ppm (2 H, d, J = 8.3 Hz, C(3)H and C(5)H); 7.34 (2 H, d, J = 8.2 Hz, C(2)H and C(6)H); 3.64 (2 H, s, CH_2).

4-(*N*-BOC-aminomethyl)phenylacetic acid

A solution of 4-cyanophenylacetic acid (12.11 g, 0.075 mol) in water (163 mL) and concentrated aqueous ammonia (40 mL) was stirred at room temperature and Raney nickel (6.3 g) was added. The resulting suspension was stuirred under a hydrogen atmosphere for 24 hours before the reaction mixture was filtered through celite and evaporated *in vacuo* to give crude 4-(aminomethyl)-phenylacetic acid (12.57 g; 100 %) as a pale blue solid.

A solution of the crude amino acid (12.57 g, 0.075 mol) in water (50 mL) and 1,4-dioxane (50 mL) was stirred at room temperature and sodium hydroxide (3 g, 0.075 mol) and di-^{t}butyl dicarbonate (16.4 g, 0.075 mol) were added simultaneously. After 24 hours the 1,4-dioxane was removed *in vacuo* and the aqueous layer was acidified with saturated aqueous citric acid (200 mL). The solution was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the *N*-BOC-amine (17.6 g, 88 %) as a white solid which was used without further purification.

^{1}H NMR ($CDCl_3$): 7.00 ppm (4 H, m, Ar); 4.65 (1 H, br s, N-H); 4.09 (2 H, d, J = 6 Hz, CH_2NH); 3.43 (2H, s, CH_2); 1.25 (9H, s, ^{t}Bu).

Methyl 4-(*N*-BOC-aminomethyl)phenylacetate

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (34.8 g, 0.18 mol) and 4-(*N*,*N*-dimethylamino)pyridine (220 mg, 1.8 mmol) were added to a solution of 4-(*N*-BOC-aminomethyl)phenylacetic acid (47.8 g,

0.18 mol) in methanol (200 ml). After stirring for 18 hours the methanol was removed *in vacuo* and the reaction mixture partitioned between ethyl acetate (200 mL) and saturated aqueous citric acid (200 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$) and evaporated to give the methyl ester (49.8 g; 99 %).

^1H NMR ($CDCl_3$): 7.42 ppm (4 H, s, Ar); 5.02 (1 H, br s, N-H); 4.48 (2 H, d, J = 5.7 Hz, CH_2NH); 3.87 (3 H, s, OMe); 3.79 (2 H, s, CH_2); 1.64 (9 H, s, ^{t}Bu).

Methyl [4-(*N*-BOC-aminomethyl)phenyl]-α-azidoacetate

A solution of methyl 4-(*N*-BOC-aminomethyl)phenylacetate (9.34 g; 0.033 mol) in THF (100 mL) was stirred under argon at -78°C and potassium bis(trimethylsilyl)amide (16.7 g, 0.084 mol) in THF (50 mL) was added. After stirring for 30 minutes, 2,4,6-triisopropylbenzene-sulfonyl azide (31.1 g, 0.101 mol) was added as a solid. After 5 minutes, acetic acid (10 mL, 0.175 mol) was added and the reaction warmed to room temperature. The reaction mixture was then partitioned between ethyl acetate (500 mL) and water (500 mL), separated and the organic layer dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by silica gel chromatography afforded the azide (7.1 g, 67 %).

^1H NMR ($CDCl_3$): 7.28 ppm (4 H, s, Ar); 4.92 (1 H, s, CHN_3); 4.25 (2 H, s, CH_2NH); 3.69 (3 H, s, OMe); 1.38 (9 H, s, ^{t}Bu).

Methyl α-amino-[4-(*N*-BOC-aminomethyl)phenylacetate

A solution of methyl [4-(*N*-BOC-aminomethyl)phenyl]-α-azidoacetate (7.1 g, 0.022 mol) in ethyl acetate (50 mL) was

stirred over palladium on carbon (5%). The reaction vessel was taken up to 250 psi with hydrogen for 17 hours. The reaction mixture was filtered through celite and evaporated *in vacuo* to give the amine (6.47 g, 100 %) as a pale solid.
^{1}H NMR ($CDCl_3$): 7.20 ppm (2 H, m, Ar); 7.12 (2 H, m, Ar); 4.81 (1 H, br s, NH); 4.45 (1 H, s, CH); 4.18 (2 H, d, J = 6 Hz, CH_2NH); 3.54 (3 H, s, OMe); 2.09 (2 H, br s, NH_2); 1.30 (9 H, s, ^{t}Bu).

Methyl α-(*N*-benzyloxycarbonyl-amino)-[4-(*N*-BOC-aminomethyl)phenyl]acetate

A solution of the amine (530 mg, 1.8 mmol) in tetrahydrofuran (15 mL) was treated with triethylamine (0.25 mL, 1.8 mmol) and benzyl chloroformate (0.26 mL, 1.8 mmol) and allowed to stir at room temperature for 1 hour. The reaction was diluted with ethyl acetate (40 mL), washed with brine (2 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil. The benzyloxycarbonyl ester was purified by flash chromatography on silica gel (ethyl acetate / hexane 1 : 1) to give a yellow solid (312 mg, 66 %).
^{1}H NMR ($CDCl_3$): 7.32 - 7.15 ppm (9 H, m, 9 Ar); 5.80 (1 H, br s, NH); 5.30 (1 H, d, J = 9.6 Hz, CH); 5.01 (2 H, s, CH_2Ph); 4.22 (2 H, d, J = 7.2 Hz, CH_2NHBoc); 3.63 (3 H, s, OCH3); 1.39 (9 H, s, ^{t}Bu).

D/L-α-(*N*-benzyloxycarbonyl)-[4-(*N*-BOC-aminomethyl)phenyl]glycine

A solution of the ester (356 mg, 0.83 mmol) in tetrahydrofuran (15 mL) was treated with 1 M LiOH (1.7 mL,

1.7 mmol) and heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue diluted with water (20 mL). The pH was reduced to 4 using 5 % aqueous HCl and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the acid as a yellow solid (273 mg, 79 %) which was carried forward without further purification.

D/L-α-(*N*-benzyloxycarbonyl)-[4-(*N*-BOC-aminomethyl)phenyl]glycine indan-5-amide.

A solution of the acid (173 mg, 0.42 mmol) in dimethylformamide (15 ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol), 1-hydroxy-7-azabenzotriazole (57 mg, 0.42 mmol), 5-aminoindane (56 mg, 0.42 mmol) and 4-(*N,N*-dimethylamino)pyridine (5 mg) and stirred overnight at room temperature before being partitioned between ethyl acetate (50 mL) and water (50 mL). The layers were separated and the organic phase was washed with 5 % aqueous HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the indanamide as a colourless solid (160 mg, 72 %) which was used without further purification.

^1H NMR ($CDCl_3$): 7.39 - 7.09 ppm (12 H, m, 10 Ar and 2 NH); 6.99 (2 H, s, Ar); 5.38 (1 H, br s, CHAr); 5.01 (2 H, s, $C\underline{H}_2Ph$); 4.81 (1 H, m, NH); 4.19 (2 H, s, $C\underline{H}_2NHBOC$); 2.85 - 2.68 (4 H, m, indane $C(1)H_2$ and $C(3)H_2$); 2.04 - 1.88 (2 H, m, indane $C(2)H_2$); 1.39 (9 H, s, ^tBu).

3-(*N*-BOC-Aminomethyl)benzoyl-D/L-4-(*N*-BOC-aminomethyl)-phenylglycine indan-5-amide

10 % Palladium on carbon (50 mg), was added to a solution of the indanamide (160 mg, 0.3 mmol) in ethanol (20 mL) and the suspension was stirred under a hydrogen atmosphere overnight . The mixture was filtered and the filter was washed with ethanol (20 ml). The combined filtrates were concentrated under reduced pressure to afford the amine as a colourless solid (107 mg, 90 %) which was carried forward without further purification.

A solution of the amine (107 mg, 0.27 mmol) in dimethylformamide (15 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (52 mg, 0.27 mmol), 1-hydroxy-7-azabenzotriazole (37 mg, 0.27 mmol), *N*-BOC-3-(aminomethyl)benzoic acid (68 mg, 0.27 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (5 mg) and stirred overnight at room temperature. The solution was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic phase was separated and washed with 5 % aqueous HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL) before being dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow solid. The residue was purified by flash chromatography on silica gel (ethyl acetate / hexane 1 : 1) to give the diprotected bis-amide as a colourless solid (103 mg, 61 %).

^1H NMR ($CDCl_3$): 9.25 ppm (1 H, s, NH); 7.94 (1 H, d, J = 7.2 Hz, Ar); 7.62 (2 H, s, Ar); 7.43 - 7.24 (5 H, m, 4 Ar, NH); 7.05 (3 H, d, J = 7.2 Hz, Ar); 6.94 (1 H, d, J = 7.2 Hz, Ar); 6.14 (1 H, d, J = 7.2 Hz, CH); 5.07 (1 H, m, NH); 4.99 (1 H, m, NH); 4.16 (2 H, s, CH_2NHBOC); 4.10 (2 H, s,

CH_2NHBOC); 2.77 - 2.61 (4 H, m, indane $C(1)H_2$ and $C(3)H_2$); 1.98 - 1.87 (2 H, m, indane $C(2)H_2$); 1.35 (9 H, s, ^tBu).

3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine indan-5-amide bis(trifluoroacetate) salt.

A solution of the diprotected bis-amide (103 mg, 0.16 mmol) in dichloromethane (5 mL) was stirred at room temperature and trifluoroacetic acid (3 mL) was added. Stirring was continued for a further hour before the solvents were removed under reduced pressure to afford the bis(trifluoroacetate) salt as a colourless solid (92 mg, 88 %).

^1H NMR (d_4 MeOH): 7.90 ppm (1 H, s, Ar); 7.84 (1 H, s, Ar); 7.65 - 7.54 (4 H, m, Ar); 7.49 - 7.32 (3 H, m, Ar); 7.12 (1 H, d, J = 7.2 Hz, Ar); 7.02 (1 H, d, J = 7.2 Hz, Ar); 5.78 (1 H, s, CHAr); 4.08 (2 H, s, CH_2NH_2); 4.01 (2 H, s, CH_2NH_2); 2.79 - 2.70 (4 H, m, indane $C(1)H_2$ and $C(3)H_2$); 2.03 - 1.90 (2 H, m, indane $C(2)H_2$).

HPLC (Luna 2, Gradient 1): rt = 3.13 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.45 minutes, 429 $(MH)^+$.

Examples 62 - 64 were prepared in a similar fashion to Example 61, using the specified amine in place of 5-aminoindane.

Example 62

3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine 1-aminoacetyl-2,3-dihydroindol-6-amide tris(trifluoroacetate salt)

Prepared from 6-amino-1-(*N*-BOC-aminoacetyl)-2,3-

dihydroindole.

^{1}H NMR (d_4 MeOH): 8.23 ppm (1 H, s, Ar); 7.84 - 7.74 (2 H, m, Ar); 7.56 - 7.30 (6 H, m, Ar); 7.17 (1 H, d, J = 7.2 Hz, Ar); 7.02 (1 H, d, J = 7.2 Hz, Ar); 5.68 (1 H, s, CHAr); 4.02 (2 H, s, CH_2NH_2); 3.99 - 3.79 (6 H, m, CH_2NH_2, dihydroindole C(2)H_2, CH_2NH_2 glycine); 3.06 - 2.97 (2 H, m, dihydroindole C(3)H_2).

HPLC (Luna 2, Gradient 1): rt = 2.13 minutes.

LCMS (Luna 2, Gradient 4): rt = 0.51 minutes, 487 $(MH)^+$.

Example 63

3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine 1-acetyl-2,3-dihydroindole bis(trifluoroacetate) salt

Prepared from 1-acetyl-6-amino-2,3-dihydroindole.

^{1}H NMR (d_4 MeOH): 8.21 ppm (1 H, s, Ar); 7.97 - 7.86 (2 H, m, Ar); 7.72 - 7.43 (6 H, m, Ar); 7.32 (1 H, d, J = 7.2 Hz, Ar); 7.12 (1 H, d, J = 7.2 Hz, Ar); 5.81 (1 H, s, CHAr); 4.17 (1 H, s, CH_2NH_2); 4.15 - 4.04 (4 H, m, CH_2NH_2, dihydroindole C(2)H_2); 3.19 - 3.07 (2 H, m, dihydroindole C(3)H_2); 2.20 (3 H, s, $NCOCH_3$).

HPLC (Luna 2, Gradient 1): rt = 2.72 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.18 minutes, 472 $(MH)^+$.

Example 64

3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine 4-(isopropyl)phenylamide bis(trifluoroacetate salt)

Prepared from 4-isopropylaniline.

^{1}H NMR (d_4 MeOH): 8.01 - 7.92 ppm (2 H, m, Ar); 7.75 - 7.43 (8 H, m, Ar); 7.18 (2 H, d, J = 9.6 Hz, Ar); 5.87 (1 H, s, CHAr); 4.21 (2 H, s, CH_2NH_2); 4.14 (2 H, s, CH_2NH_2); 2.96 -

2.81 (1 H, m, $CH(CH_3)_2$); 1.24 (6 H, d, J = 7 Hz, $CH(CH_3)_2$).
HPLC (Luna 2, Gradient 1): rt = 3.39 minutes.
LCMS (Luna 2, Gradient 4): rt = 1.59 minutes, 431 $(MH)^+$.

Examples 65 - 68 were prepared in a similar manner to Example 61 except that the indicated protected amino acid was used in the place of D/L-4-(*N*-BOC-aminomethyl)-α-(*N*-benzyloxycarbonyl)phenylglycine.

Example 65

3-(Aminomethyl)benzoyl-D-cyclohexylglycine indan-5-amide trifluoroacetate salt

Prepared from *N*-BOC-D-cyclohexylglycine.
^1H NMR (d_4 MeOH): 7.88 - 7.02 ppm (7 H, m, Ar); 4.43 (1 H, d, J = 9 Hz, CH(cHex)); 4.04 (2 H, s, CH_2NH_2); 2.78 - 2.68 (4 H, m, indane $C(1)H_2$ and $C(3)H_2$); 2.04 - 1.82 (4 H, m, indane $C(2)H_2$, cHex CH_2); 1.77 - 1.56 (4 H, m, 2 x cHex CH_2); 1.36 - 0.95 (5 H, m, 2 x cHex CH_2 and CH).
HPLC (Luna 2, Gradient 1): rt = 4.27 minutes.
LCMS (Luna 2, Gradient 4): rt = 2.21 minutes, 406 $(MH)^+$.

Example 66

3-(Aminomethyl)benzoyl-D/L-1-naphthylglycine indan-5-amide trifluoroacetate salt

Prepared from *N*-BOC-D/L-1-naphthylglycine.
^1H NMR (d_4 MeOH): 8.25 ppm (1 H, d, J = 7.2 Hz, Ar); 8.04 - 7.84 (4 H, m Ar); 7.75 - 7.44 (7 H, m, Ar); 7.33 (1 H, d, J = 7.25 Hz, Ar); 7.16 (1 H, d, J = 7.25 Hz, Ar); 6.72 (1 H, s, CHAr); 4.15 (2 H, s, CH_2NH_2); 2.94 - 2.78 (4 H, m, indane $C(1)H_2$ $C(3)H_2$); 2.17 - 1.98 (2 H, m, indane $C(2)H_2$).

HPLC (Luna 2, Gradient 1): rt = 4.37 minutes.
LCMS (Luna 2, Gradient 4): rt = 2.37 minutes, 450 $(MH)^+$.

Example 67

3-(Aminomethyl)benzoyl-D/L-(4-phenyl)phenylglycine indan-5-amide trifluoroacetate salt

Prepared from *N*-Fmoc-D/L-(4-phenyl)phenylglycine.
^1H NMR (d_4 MeOH): 7.94 - 7.83 ppm (2 H, m, Ar); 7.64 - 7.15 (13 H, m, Ar); 7.02 (1 H, d, J = 7.2 Hz, Ar); 5.80 (1 H, s, CH); 4.08 (2 H, s, CH_2NH_2); 2.81 - 2.77 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.01 - 1.88 (2 H, m, indane C(2)H_2).
HPLC (Luna 2, Gradient 1): rt = 4.87 minutes.
LCMS (Luna 2, Gradient 4): rt = 2.56 minutes, 476 $(MH)^+$.

Example 68

3-(Aminomethyl)benzoyl-D-(4-aminophenyl)glycine indan-5-amide bis(trifluoroacetate) salt

Prepared from *N*-BOC-D-(4-Benzyloxycarbonylaminophenyl)-glycine (prepared as described below).

D-(4-Hydroxyphenyl)glycine methyl ester hydrochloride

D-4-Hydroxyphenylglycine (12.5 g, 74.8 mmol) and dry methanol (24 mL) were stirred in a dry 250 mL three necked round bottom flask, equipped with a low temperature thermometer. The mixture was stirred under nitrogen and cooled to an internal temperature of below -20°C. Using a syringe, thionyl chloride (6 mL, 9,78 g, 82.2 mmol) was added dropwise to the cooled mixture over a period of 10 minutes at such a rate that the internal temperature did not exceed -20°C. Once the addition was complete the mixture

was allowed to warm to room temperature and stirred overnight. Dry ether (150 mL) was added and the white precipitate that formed was collected by suction filtration, washed with a little more ether and dried (15.5g, 95%).

N-BOC-D-(4-Hydroxyphenyl)glycine methyl ester

Di-t-butyl dicarbonate (15.9 g, 72.8 mmol) was added to a stirred mixture of D-4-hydroxyphenylglycine methyl ester hydrochloride (14 g, 64.3 mmol) and $NaHCO_3$ (11.7 g, 0.14 mol) in tetrahydrofuran (150 mL) and water (50 mL), in one portion. The mixture was stirred rapidly for 4h. Hexane (75 mL) was added and the organic layer separated and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded the *N*-BOC-protected amine (19.7g, 96%).

N-BOC-D-(4-Trifluoromethylsulphonyloxyphenyl)glycine methyl ester

2,6-Lutidine (9.44 ml, 8.68 g, 81.0 mmol) and 4-dimethylaminopyridine (1.65 g, 13.5 mmol) were added to a stirred solution of *N*-BOC-D-(4-hydroxyphenyl)glycine methyl ester (19 g, 67.5 mmol) in dichloromethane (400 mL) and the mixture cooled in an ice bath. Trifluoromethananesulphonic anhydride (13.7 mL, 23.0 g, 81.4 mmol) was added over a period of five minutes and then the mixture was allowed to warm to room temperature over four hours. The solution was washed with water (2 x 150 mL), 1N HCl (2 x 150 mL) and saturated aqueous $NaHCO_3$ (150 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded an oil which was purified by flash chromatography on silica gel (hexane /

dichloromethane 1:1 and then neat dichloromethane) affording the triflate as a white solid (19 g, 77%).

***N*-BOC-D-(4-benzyloxycarbonylphenyl)glycine methyl ester**

N-BOC-D-(4-trifluoromethylsulphonyloxyphenyl)glycine methyl ester (27.6 g, 77.0 mmol), benzyl alcohol (32.6 mL, 34.1 g, 315 mmol), palladium (II) acetate (255 mg, 1.13 mmol), bis-1,3-diphenylphosphinylpropane (448 mg, 1.09 mmol) and triethylamine (10.2 mL, 7.40 g, 73.2 mmol) in dimethylformamide (72 mL) were placed in a Parr reactor and the reactor assembled. The vessel was pressurised to ~10 psi with nitrogen and the gas released (repeated five times to remove all oxygen from the system). Carbon monoxide gas was then carefully introduced to ~20 psi and released three times. Carbon monoxide was then added to ~100 psi and the stirrer started. The vessel was slowly heated to 65 °C internal temperature and then stirred, monitoring by tlc. When complete (after ~ 18 hours) the reaction was cooled to 30°C, the gas released and the vessel flushed five times with nitrogen as before. The reaction mixture was partitioned between ethyl acetate (250 mL) and water (100 mL) and the organic layer washed with 1M hydrochloric acid (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) and dried ($MgSO_4$) and evaporated. Purification of the resulting oil by column chromatography (ethyl acetate / hexane; 1:4) gave the benzyl ester (18.7 g, 70%).

***N*-BOC-D-(4-hydroxycarbonylphenyl)glycine methyl ester**

10 % Palladium on carbon (100 mg) was added to a solution of the benzyl ester (500 mg, 1.25 mmol) in ethanol (15 mL) and

the suspension was stirred under a hydrogen atmosphere overnight. The mixture was filtered and the residue was washed with ethanol (20 mL) and the combined organic solvents were evaporated under reduced pressure to afford the acid as a colourless solid (363 mg, 94 %).
^{1}H NMR ($CDCl_3$): 8.08 ppm (2 H, br s, Ar); 7.49 (2 H, d, J = 7.2 Hz, Ar); 5.87 (1 H, d, J = 9 Hz, NHCH); 3.73 (3 H, s, OCH_3); 1.41 (9 H, s, ^{t}Bu).

***N*-BOC-D-(4-Benzyloxycarbonylaminophenyl)glycine methyl ester.**

The acid (218 mg, 0.7 mmol) in tetrahydrofuran (20 mL) was treated with triethylamine (108 µl, 0.78 mmol) and diphenylphosphonic azide (161 µl, 0.78 mmol) and stirred at room temperature for 1.5 hours. Benzyl alcohol (116 µl, 1.12 mmol) was then added and the mixture was heated at reflux for 18 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate / hexane, 1:1) to give the *N*-benzyloxycarbonylaniline as a brown solid (87 mg, 30 %).
^{1}H NMR ($CDCl_3$): 7.35 - 7.23 ppm (7 H, m, Ar); 7.16 (2 H, d, J = 9 Hz, Ar); 7.06 (1 H, s, NH); 5.53 (1 H, d, J = 9 Hz, CHAr); 5.18 (1 H, d, J = 9 Hz, NH); 5.10 (2 H, s, CH_2Ph); 3.59 (3 H, s, OCH_3); 1.31 (9 H, s, ^{t}Bu).

***N*-BOC-D-(4-Benzyloxycarbonylaminophenyl)glycine**

A solution of the ester (87 mg, 0.21 mmol) in tetrahydrofuran (5 mL) was treated with 1 M LiOH (0.84 ml, 0.84 mmol) and heated at reflux for four hours. The solvent was removed under reduced pressure and the residue was

diluted with water (10 mL). The aqueous solution was acidified to pH 4 using 5 % aqueous HCl and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude acid (80 mg, 95 %) as a colourless solid which was carried forward without further purification.

3-(Aminomethyl)benzoyl-D-(4-aminophenyl)glycine indan-5-amide bis(trifluoroacetate) salt.

^1H NMR (d_4 MeOH): 7.92 - 7.80 ppm (2 H, m, Ar); 7.69 (2 H, d, J = 7.3 Hz, Ar); 7.60 - 7.40 (2 H, m, Ar); 7.34 (3 H, d, J = 12 Hz, Ar); 7.15 (1 H, d, J = 7.2 Hz, Ar); 7.02 (1 H, d, J = 7.2 Hz, Ar); 5.79 (1 H, s, CHAr); 4.07 (2 H, s, CH_2NH_2); 2.80 - 2.69 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.01 - 1.88 (2 H, m, indane C(2)H_2).

HPLC (Luna 2, Gradient 1): rt = 3.17 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.59 minutes, 415 $(MH)^+$.

Example 69

3-(Aminomethyl)benzoyl-D/L-piperidin-4-ylglycine indan-5-amide bis(trifluoroacetate) salt

(*N*-BOC-Piperidin-4-ylidene)-(*N*-benzyloxycarbonyl)glycine methyl ester

N-BOC-4-Piperidone (2.0 g, 10 mmol), *N*-(benzyloxy-carbonyl)-α-phosphonoglycine trimethyl ester (3.64 g, 2.20 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.57 mL, 2.10 mmol) were stirred in acetonitrile overnight. The solvent was removed and the residue taken up in ethyl acetate (50 mL) and washed with water (2 x 10 mL), dried ($MgSO_4$) and evaporated under

reduced pressure. The residual oil was purified by chromatography on silica gel (ethyl acetate / hexane, 40 % / 60 %) to afford the unsaturated ester (3.63 g, 90 %). ^{1}H NMR ($CDCl_3$): 7.36 ppm (5 H, br s, Ph); 6.05 (1 H, br s, NH); 5.12 (2 H, s, CH_2Ph); 3.73 (3 H, br s, OMe); 3.50 (4 H, br s, piperidine C(2)H_2 and C(6)H_2); 2.86 (2 H, br s, piperidine C(3) H_2 or C(5) H_2); 2.45 - 2.36 (2 H, m, piperidine C(3) H_2 or C(5) H_2); 1.47 (9 H, s, ^{t}Bu).

(*N*-BOC-Piperidin-4-ylidene)-(*N*-benzyloxycarbonyl)glycine

A solution of the methyl ester (391 mg, 1 mmol) in tetrahydrofuran (10 mL) was treated with 1 M LiOH (2 mL, 2 mmol) and heated at reflux for 4 hours. The solvent was removed under reduced pressure and the residue diluted with water (20 mL). The aqueous solution was acidified to pH 4 with 5 % aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the acid as a brown solid (305 mg, 78 %) which was carried forward without further purification.

(*N*-BOC-Piperidin-4-ylidene)-(*N*-benzyloxycarbonyl)glycine indan-5-amide

A solution of the acid (253 mg, 0.65 mmol) in dimethylformamide (20 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (124 mg, 0.65 mmol), 1-hydroxy-7-azabenzotriazole (88 mg, 0.65 mmol), 5-aminoindane (86 mg, 0.65 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg) and stirred overnight at room temperature. The solution was partitioned between ethyl

acetate (30 mL) and water (30 mL), separated, and the organic phase was washed with 5 % aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless solid. The crude product was purified by flash chromatography (ethyl acetate / hexane 1 : 1) to afford the indanamide as a colourless solid (215 mg, 65 %).
^1H NMR ($CDCl_3$): 8.31 (1 H, br s, NH); 7.43 (9 H, m, 8 Ar, NH); 5.01 (2 H, s, CH_2Ph); 3.34 (4 H, br s, piperidine C(2)H_2 and C(6)H_2); 2.83 - 2.71 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.54 (2 H, br s, piperidine C(3)H_2 or C(5)H_2); 2.23 - 2.14 (2 H, m, piperidine C(3)H_2 or C(5)H_2); 2.05 - 1.92 (2 H, m, indane C(2)H_2); 1.38 (9 H, s, ^{t}Bu).

D/L-(*N*-BOC-Piperidin-4-yl)glycine indan-5-amide

10 % Palladium on carbon (50 mg) was added to a solution of the alkene (215 mg, 0.43 mmol) in ethanol (20 mL) and the suspension was stirred under a hydrogen atmosphere overnight. The mixture was filtered and the filtrand was washed with ethanol (20 ml) before the combined solvents were concentrated under reduced pressure to afford the deprotected saturated amine as a colourless oil (97 mg, 60 %). The crude amine was carried forward without further purification.

The remaining steps of the synthesis are identical to those of Example 61.

3-(Aminomethyl)benzoyl-D/L-piperidin-4-ylglycine indan-5-amide bis(trifluoroacetate) salt.

^{1}H NMR (d_4 MeOH): 8.04 - 7.92 ppm (2 H, m, Ar); 7.73 - 7.55 (2 H, m, Ar); 7.49 (1 H, s, Ar); 7.32 (1 H, d, *J* = 7.2 Hz, Ar); 7.18 (1 H, d, *J* = 7.2 Hz, Ar); 4.68 (1 H, d, *J* = 9 Hz, C<u>H</u>(Pip)); 4.21 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.54 - 3.40 (2 H, m, piperidine C(2)H and C(6)H); 3.13 - 2.96 (2 H, m, piperidine C(2)H and C(6)H); 2.94 - 2.81 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.41 - 2.23 (1 H, m, piperidine C(4)H); 2.20 - 1.95 (4 H, m, indane C(2)H_2, piperidine C(3)H and C(4)H); 1.84 - 1.60 (2 H, m, piperidine C(3)H and C(4)H).

HPLC (Luna 2, Gradient 1): rt = 3.08 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.27 minutes, 407 $(MH)^+$.

Example 70

2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide bis(trifluoroacetate) salt

2-Amino-5-cyanobenzoic acid

A solution of 2-amino-5-bromobenzoic acid (6.9 g, 31.9 mmol) in *N*-methyl-2-pyrrolidinone (100 mL) was treated with copper cyanide (4.14 g, 46 mmol) and the mixture was heated at 190°C for 4.5 hours before being cooled to room temperature and allowed to stand overnight. The mixture was diluted with water (500 mL), acidified with 6N aqueous HCl (100 mL) and extracted with ethyl acetate (6 x 40 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude nitrile (4.35 g, 84 %).

2-Amino-5-cyanobenzoyl-D-phenylglycine methyl ester

A solution of 2-amino-5-cyanobenzoic acid (1.0 g, 6.17 mmol) in dimethylformamide (50 mL) was treated with 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g, 6.17 mmol) and 1-hydroxy-7-azabenzotriazole (0.84 g, 6.17 mmol). After stirring for 10 minutes, D-phenylglycine methyl ester (1.24 g, 6.17 mmol) was added and the resulting solution was stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL) and the organic solution was washed with saturated aqueous citric acid (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate / hexane, 1:1) to yield 2-amino-5-cyanobenzoyl-D-phenylglycine methyl ester (1.3 g, 68 %).

LC/MS (Luna 2, Gradient 4): rt = 3.28 minutes, 310 $(MH)^+$.

2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine methyl ester

A solution of 2-amino-5-cyanobenzoyl-D-phenylglycine methyl ester (800 mg, 2.6 mmol) in dimethylformamide (20 mL) was treated with 4-dimethylaminopyridine (30 mg; 0.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (500 mg; 2.6 mmol) and di-t-butyldicarbonate (570 mg; 2.6 mmol). The mixture was stirred overnight at room temperature and then partitioned between ethyl acetate (25 mL) and water (25 mL). The organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate / hexane 3:7) to yield the bis-protected amine (150 mg, 11 %).

2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine

The ester (150 mg, 0.29 mmol) was dissolved in tetrahydrofuran (20 mL) and treated with 1 M lithium hydroxide (0.6 mL, 0.6 mmol). The mixture was heated at reflux for 3 hours, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (10 mL), acidified with 5% aqueous HCl (10 mL) and the product extracted into ethyl acetate (25 mL). The organic extracts were then dried ($MgSO_4$) and concentrated under reduced pressure and the crude acid (110 mg, 75 %) was carried forward without further purification.

2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine indan-5-ylamide

A solution of the acid (110 mg, 0.20 mmol) in dimethylformamide (10 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg, 0.2 mmol) and 1-hydroxy-7-azabenzo-triazole (30 mg, 0.2 mmol). After stirring for 10 minutes, 5-aminoindane (30 mg, 0.2 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and water (25ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate / hexane, 3:7) to yield 2-(di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine indan-5-ylamide as an off-white solid (50 mg, 40 %).

2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-

ylamide bis(trifluoroacetate) salt.

A solution of the nitrile (50 mg, 0.08 mmol) in methanol (10 mL) and 36% aqueous HCl (0.5ml) was stirred over 10% palladium on carbon (20 mg) under a hydrogen atmosphere for 16 hours. The mixture was filtered and the residue was washed with methanol (10 mL) before concentrating the extracts under reduced pressure.

The residue was dissolved in a mixture of trifluoroacetic acid (5 ml) and dichloromethane (5ml) and stirred for one hour. The mixture was concentrated under reduced pressure and the residue purified by preparative HPLC to afford 2-amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide ditrifluoroacetate salt (2 mg, 6 %).

^{1}H NMR (d_4 MeOH): 7.98-7.37 ppm (10 H, m, Ar); 7.02 (1H, d, *J* = 7.5 Hz, Ar); 6.03 (1H, s, C<u>H</u>Ph); 3.92 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.09 (4H, q, *J* = 7.5Hz, indane C(1)H$_2$ and C(3)H$_2$); 2.29 (2H, quintet, *J* = 7.5 Hz, indane C(2)H$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.04 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 398 $(MH-NH_3)^+$.

Example 71

1-(2-Amino-5-(aminomethyl)benzoyl-D-phenylglycinyl) 4-hydroxypiperidine dihydrochloride salt

D-Phenylglycine 4-hydroxypiperidinamide trifluoroacetate salt

A solution of 4-hydroxypiperidine (330 mg, 1.4 mmol) in dimethylformamide (10 mL) was treated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (450 mg; 1.4 mmol) and *N*-

ethyldiisopropylamine (0.74 mL, 4.2 mmol). After stirring for 10 minutes, *N*-butoxycarbonyl-D-phenylglycine (330 mg, 1.4 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous NaHCO3 (25 mL) and water (25 mL), dried (MgSO4) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) and stirred for one hour before the solvents were removed under reduced pressure, giving D-phenylglycine-4-hydroxypiperidinamide as its trifluoracetate salt (150 mg, 43 %).

LC/MS (Luna 2, Gradient 4): rt = 2.64 min, 235 $(MH)^+$.

2-amino-5-cyanobenzoyl-D-phenylglycine 4-hydroxypiperidinamide

A solution of 2-amino-5-cyanobenzoic acid (170 mg, 1.0 mmol) in dimethylformamide (10 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (210 mg, 1.1 mmol) and 1-hydroxy-7-azabenzotriazole (150 mg, 1.1 mmol). After stirring for 10 minutes, D-phenylglycine 4-hydroxypiperidinamide trifluoroacetate salt (250 mg; 1.1 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl

acetate) to yield 2-amino-5-cyanobenzoyl-D-phenylglycine 4-hydroxypiperidinamide (90 mg, 23 %).

1-(2-amino-5-(aminomethyl)benzoyl-D-phenylglycinyl 4-hydroxypiperidine dihydrochloride salt

A solution of the nitrile in methanol (10 mL) and 36% hydrochloric acid (0.5 mL) was stirred over 10 % palladium on carbon (20 mg) under an atmosphere of hydrogen for 16 hours. The mixture was filtered and the residue washed with methanol (10 mL) before concentrating the filtrate under reduced pressure. Purification by preparative HPLC afforded 2-amino-5-(aminomethyl)benzoyl-D-phenylglycine 4-hydroxy-piperidinamide dihydrochloride salt (30 mg, 33 %).

^{1}H NMR (d_4 MeOH): 7.84 ppm (1 H, s, Ar); 7.61-7.17 (7 H, m, Ar); 6.85 (1 H, d, J = 8 Hz, Ar); 6.12 (1 H, s, C$\underline{H}$Ph); 4.26 (1 H, m, piperidine C(4)H); 3.99 (2 H, s, C$\underline{H}_2$NH$_2$); 3.79 (2 H, m, piperidine C(2)H and C(6)H); 3.42-3.08 (2H, m, piperidine C(2)H and C(6)H); 1.86-0.72 (4H, m, piperidine C(3)H$_2$ and C(5)H$_2$).

HPLC (Luna 2, Gradient 1): rt = 2.49 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 366 $(MH-NH_3)^+$.

Examples 72 and 73

The compounds of Examples 72 and 73 were prepared by the method described below, but using the appropriate starting materials.

Boc D-phenylglycine (251 mg, 1 mmol.) was dissolved in dimethylformamdide (3ml) with HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (380

mg., 1 mmol.) and diisopropylethylamine (350µl., 2 mmol.). To this mixture was added 4-methylbenzylamine (121mg., 1 mmol.) and diisopropylethylamine (170µl., 1 mmol.). The mixture was stirred overnight. The mixture was then taken up into ethylacetate and washed with water, sodium carbonate solution, water, 10% hydrochloric acid solution and water. The ethylacetate was evaporated without drying and treated immediately with trifluoroacetic acid (TFA) for 30 min. The TFA was then evaporated to dryness and the product triturated with diethylether. Triethylamine (1ml) was added and evaporated to dryness. A solution of 3-hydroxymethylbenzoic acid (76mg, 0.5mmole) in dry dimethylformamide (DMF) was treated with TBTU (161mg., 0.5mmol.) and diisopropylethylamine (1.5 mmol.). The mixture was then added to the D-phenylglycine-4-methylbenzylamide (0.5mmol.) and stirred overnight. The crude product was dissolved in water/acetonitrile (20ml), filtered and purified by preparative Hplc to yield pure product.
^{1}H nmr (CD_3CN) 7.75 (1H, m); 7.65 (2H, m); 7.30 (7H, broad m); 6.80 (3H, m); 5.40 (1H, s); 4.45 (2H,s); 4.10 (2H, m); 2.10 (3H, s). MS TOF 389 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.51 min.

Compounds made by the above method:-

Example 72.

3-Aminomethylbenzoyl-D-phenylglycine-4-aminomethylcyclohexyl methylamide

^{1}H nmr (CD_3CN) 7.95 (2H, m); 7.80 (2H, m); 7.50 (5H, m); 5.65 (1H, s); 4.45 (2H, s); 3.30 (2H, m); 3.00 (2H,m); 2.00-1.00

(10H,m). MS TOF 409 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.68 min.

Example 73.

3-Aminomethylbenzoyl-D-phenylglycine-1-adamantylamide

^{1}H nmr (CD_3CN) 7.95 (1H, s); 7.85 (2H, d); 7.60 (1H, m); 7.50 (2H,m); 7.40 (3H,m); 5.65 (1H, s); 4.20 (2H, s); 2.50-1.50 (15H,m). MS TOF 418 (M+1$^+$). Hplc (Magellan C8, Gradient 1, water/acetonitrile/TFA) rt 18.36 min.

Example 74

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.

Prepared in a similar manner to Example 35, using (2-hydroxyphenyl)acetic acid.

^{1}H NMR (CD_3CN): 8.91 ppm (1 H, s, OH), 8.30 (1 H, s, NH), 7.94 (2 H, br s, Ar), 7.73 (1 H, d, J = 10 Hz, Ar), 7.54-7.06 (12 H, m, Ar & NH), 7.01 (1 H, d, J = 8 Hz, Ar), 6.74 (2 H, m, Ar), 5.61 (1 H, d, J = 8 Hz, ArC$\underline{H}$), 4.21 (2 H, t, J = 8 Hz, dihydroindole C(2)H_2), 4.10 (2 H, s, ArC$\underline{H}_2$N), 3.73 (2H, s, ArC$\underline{H}_2$CO), 3.10 (2 H, d, J = 8 Hz, dihydroindole C(3)H_2).

HPLC (Symmetry, Gradient 2): rt = 6.24 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 535 (MH)$^+$.

Example 75

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.

Prepared in a similar manner to Example 35, using (3-hydroxyphenyl)acetic acid.

^{1}H NMR (d_4 MeOH): 8.21 ppm (1 H, s, Ar), 7.71 (2 H, br s, Ar), 7.50-7.16 (8 H, m, Ar), 7.05-6.95 (2 H, m, Ar), 6.64-6.50 (3 H, m, Ar), 5.62 (1 H, s, ArC<u>H</u>), 4.09 (2 H, s, ArC<u>H</u>$_2$N), 4.04 (2 H, t, J = 8 Hz, dihydroindole C(2)H$_2$), 3.68 (2H, s, ArC<u>H</u>$_2$CO), 2.91 (2 H, d, J = 8 Hz, dihydroindole C(3)H$_2$).

HPLC (Symmetry, Gradient 2): rt = 5.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 535 (MH^+).

Example 76

3-(Aminomethyl)benzoyl-D-phenylglycine 1-(4-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.

Prepared in a similar manner to Example 35, using (4-hydroxyphenyl)acetic acid.

^{1}H NMR (d_4 MeOH): 8.32 ppm (1 H, s, Ar), 8.04 (2 H, br s, Ar), 7.66-7.34 (8 H, m, Ar), 7.22-7.11 (3 H, m, Ar), 6.80 (2 H, d, J = 10 Hz, Ar), 5.85 (1 H, s, ArC<u>H</u>), 4.21 (2 H, s, ArC<u>H</u>$_2$N), 4.15 (2 H, t, J = 8 Hz, dihydroindole C(2)H$_2$), 3.81 (2 H, s, ArC<u>H</u>$_2$CO), 3.20 (2 H, d, J = 8 Hz, dihydroindole C(3)H$_2$).

HPLC (Symmetry, Gradient 2): rt = 5.97 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.02 minutes, 535 (MH^+).

Example 77

3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-acetylindol-5-amide trifluoroacetate salt.

Prepared in a similar fashion to Example 1, starting from

3-acetyl-5-amino-1-benzylindole, which was prepared as described below.

3-Acetyl-5-nitroindole and 3-acetyl-7-nitroindole

Prepared by the method described by Ottoni, Cruz and Kramer in *Tetrahedron Letters*, **40**, 1999, 1117-1120, as a mixture of isomers.

3-Acetyl-1-benzyl-5-nitroindole and 3-acetyl-1-benzyl-7-nitroindole

Potassium carbonate (940 mg, 6.8 mmol) was added to a stirred solution of the above indoles (695 mg, 3.4 mmol) in dimethylformamide (30 mL). Benzyl bromide (0.61 mL, 5.1 mmol) was then added dropwise and the mixture left to stir over the weekend. The dimethylformamide was removed under reduced pressure and the residue partitioned between ethyl acetate (30 mL) and water (20 mL). The ethyl acetate layer was dried ($MgSO_4$) and evaporated to give the benzylamines as a golden oil.

3-Acetyl-5-amino-1-benzylindole and 3-acetyl-7-amino-1-benzylindole

A mixture of the indoles (1.0 g, 3.4 mmol), tin(II) chloride dihydrate (3.48 g, 15.4 mmol) and ethanol (20 mL) was heated at reflux, under an atmosphere of nitrogen, for 3 hours. The mixture was cooled and the solvent evaporated to give a brown oil. To this was added water (50 mL), which was then

made basic with 1 N aqueous sodium hydroxide. The aqueous solution was then extracted with ethyl acetate (2 x 30 mL). The whole biphasic mixture was filtered through celite to remove tin salts, separated and the organic solvent dried ($MgSO_4$). The solvent was removed under reduced pressure to give a brown oil which was purified by flash chromatography on silica gel (hexane / ethyl acetate; 3:1)to afford, in order of elution,

3-acetyl-7-amino-1-benzylindole

^1H NMR ($CDCl_3$): 7.67 ppm (1 H, s, indole C(2)H); 7.39 - 7.13 (3 H, m, Ph); 7.15 (2 H, m, Ph); 7.05 (1 H, t, J = 6 Hz, indole C(5)H); 6.57 (1 H, d, J = 6.5 Hz, indole C(4)H); 6.41 (1 H, d, J = 6 Hz, indole C(6)H); 5.95 (2 H, br s, NH_2); 5.27 (2 H, s, $PhC\underline{H}_2$); 2.50 (3 H, s, CH_3)

and **3-acetyl-5-amino-1-benzylindole**

^1H NMR ($CDCl_3$): 8.08 ppm (1 H, d, J = 6 Hz, indole C(7)H); 7.50 (1 H, s, indole C(2)H); 7.31 - 7.22 (3 H, m, Ph); 7.05 (2 H, m, Ph); 6.63 (1 H, dd, J = 6, 2 Hz, indole C(6)H); 6.45 (1 H, s, indole 4-H); 5.25 (2 H, s, $PhC\underline{H}_2$); 3.62 (2 H, br s, NH_2); 2.5 (3 H, s, CH_3).

3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-acetylindol-5-amide trifluoroacetate salt.

^1H NMR (d_4 MeOH): 8.28 ppm (1 H, s, Ar); 8.20 (1 H, d, J = 5 Hz, Ar); 7.97 (3 H, m, Ar); 7.71 - 7.56 (4 H, m, Ar); 7.47 - 7.19 (9 H, m, Ar); 5.85 (1 H, s, $C\underline{H}Ph$); 5.45 (2 H, s, $C\underline{H}_2Ph$); 4.21 (2 H, $C\underline{H}_2NH_2$); 2.53 (3 H, s, CH_3).

HPLC (Luna 2, Gradient 1): rt = 4.15 minutes.

HPLC (Symmetry, Gradient 2): rt = 6.77 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.48 minutes, 531 $(MH)^+$.

Example 78

3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-acetylindol-7-amide trifluoroacetate salt.

Prepared in a similar fashion to Example 1, starting from 3-acetyl-7-amino-1-benzylindole, which was prepared as described above.

^1H NMR (d_4 MeOH): 8.46 ppm (1 H, s, Ar); 8.34 (1 H, d, J = 6 Hz, Ar); 8.11 - 7.95 (3 H, m, Ar); 7.75 - 7.48 (4 H, m, Ar); 7.46 - 7.12 (9 H, m, Ar); 5.85 (1 H, s, C$\underline{H}$Ph); 5.48 (2 H, s, C$\underline{H}_2$Ph); 4.21 (2 H, s, C$\underline{H}_2$NH$_2$); 2.62 (3 H, s, C$\underline{H}_3$).

HPLC (Luna 2, Gradient 1): rt = 4.58 minutes.

HPLC (Symmetry, Gradient 2): rt = 6.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.80 minutes, 531 $(MH)^+$.

Example 79

3-(Aminomethyl)benzoyl-D-(4-hydroxyphenyl)glycine indan-5-amide trifluoroacetate salt.

Prepared in a similar fashion to Example 61, using (4-hydroxyphenyl)glycine and protecting as appropriate.

^1H NMR (d_4 MeOH): 8.00 ppm (2 H, s, Ar); 7.72 - 7.55 (2 H, m, Ar); 7.47 (3 H, t, J = 8.6 Hz, Ar); 7.31 (1 H, d, J = 7.5 Hz, Ar); 7.18 (1 H, d, J = 8 Hz, Ar); 6.86 (2 H, d, J = 8.6 Hz, Ar); 5.75 (1 H, s, C$\underline{H}$Ph); 4.23 (2 H, s, C$\underline{H}_2$NH$_2$); 2.94 (4 H, m, indane C(1)$\underline{H}_2$ and C(3)$\underline{H}_2$); 2.12 (2 H, m, indane C(2)$\underline{H}_2$).

HPLC (Luna 2, Gradient 1): rt = 3.78 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 416 $(MH)^+$.

Example 80

3-(Aminomethyl)benzoyl-D/L-2-(*N*-formylamino)thiazol-4-yl]glycine 5-indanamide trifluoroacetate salt

Prepared using the same method as described for Example 61 from D/L-α-(*N*-^{t}butyloxycarbonyl)-[2-(*N*-formylamino)thiaz-4-yl]glycine (synthesised as described below).

Ethyl α-azido-[2-(N-formylamino)thiaz-4-yl]acetate

A solution of ethyl [2-(*N*-formylamino)thiaz-4-yl]acetate (1 g, 0.0047 mol) in THF (10 mL) was stirred under argon at -78°C and potassium bis(trimethylsilyl)amide (2.8 g, 0.014 mol) in THF (10 mL) was added. After stirring for 30 minutes, 2,4,6-triisopropylbenzenesulfonyl azide (3.6 g, 0.012 mol) was added as a solid in one portion. After 5 minutes, acetic acid (1.4 mL, 0.018 mol) was added and the mixture warmed to room temperature. The reaction mixture was then partitioned between ethyl acetate (100 mL) and water (100 mL), separated and the organic layer dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by silica gel chromotography afforded the azide (0.95 g, 80 %).

^{1}H NMR ($CDCl_3$): 8.78 ppm (1 H, s, NHC<u>H</u>O); 6.98 (1 H, s, C(5)H); 5.95 (1 H, s, C<u>H</u>N_3); 4.18 (2 H, m, C<u>H_2</u>CH_3); 1.20 (3 H, m, CH_2C<u>H_3</u>).

Ethyl α-(*N*-^{t}butyloxycarbonylamino)-[2-(*N*-formylamino)thiaz-

4-yl]acetate

Di-^{t}butyl dicarbonate (0.9 g, 0.004 mol) and 5% palladium on carbon (catalytic amount) were added to a solution of the azide (0.95 g, 0.0037 mol) in methanol (25 mL). The mixture was stirred at room temperature under an atmosphere of hydrogen for 8 hours. After this time the mixture was filtered through celite, washing through with methanol (25 mL). Evaporation of the solvent and purification of the residue by silica gel chromotography afforded the ^{t}butyloxycarbonyl amine as a pale oily solid (1.1 g, 90 %)

^{1}H NMR ($CDCl_3$): 8.53 ppm (1 H, s, NHC<u>H</u>O); 6.89 (1 H, s, C(5)H); 6.18 (1 H, d, *J* = 8 Hz, N<u>H</u>Boc); 5.38 (1 H, d, *J* = 8 Hz, C<u>H</u>N); 4.06 (2 H, m, $C\underline{H}_2CH_3$); 1.28 (9 H, s, tBu); 1.12 (3 H, m, $CH_2C\underline{H}_3$).

D/L-α-*N*-^{t}butyloxycarbonyl-[2-(*N*-formylamino)thiaz-4-yl]glycine

A solution of the ester (1.1 g, 0.0031 g) in THF (25 mL) was treated with 1 M aqueous LiOH (5 ml, 0.005 mol) and heated at reflux for 1 hour. The solvent was removed under reduced pressure and the residue diluted with water (100 mL). The pH was reduced to 2 using 5% aqueous HCl and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the acid as a white solid (0.8 g, 84 %).

^{1}H NMR (d_4 MeOH): 8.38 ppm (1 H, s, NHC<u>H</u>O); 7.01(1 H, s, C(5)H); 5.21 (1 H, s, C<u>H</u>N); 1.39 (9 H, s, ^{t}Bu).

3-(Aminomethyl)benzoyl-D/L-[2-(formylamino)thiazol-4-

yl]glycine 5-indanamide trifluoroacetate salt

^{1}H NMR (d_4 MeOH): 10.10 ppm (1 H, s, NHCHO); 8.80 (1 H, d, *J* = 8 Hz, NH); 8.48 (1 H, s, NHCHO); 7.97 (2 H, br s, Ar); 7.58 (2 H, m, Ar); 7.42 (1 H, s, aminothiazole C(5)H); 7.37 (1 H, d, *J* = 7 Hz, indane C(6)H); 7.18 (1 H, s, indane C(4)H); 7.10 (1 H, d, *J* = 7Hz, indane C(7)H); 5.92 (1 H, m, CHAr); 4.18 (2 H,s, CH_2NH_2); 2.83 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.02 (2 H, m, indane C(2)H_2)

HPLC (Luna 2, gradient 1): rt = 3.71 minutes.

LC/MS (Luna 2, gradient 4): rt = 2.05 minutes; 450 $(MH)^+$.

Example 81

3-(Aminomethyl)benzoyl-D/L-2-aminothiazol-4-ylglycine-5-indanamide bis(hydrochloride) salt.

Prepared from D/L-α-*N*-^{t}butyloxycarbonyl-[2-(*N*-formylamino)thiaz-4-yl]glycine and synthesised using the method of Example 80 except that the final deprotection was effected using 3 M aqueous HCl in THF, in order to remove both the ^{t}butyloxycarbonyl and formyl protecting groups.

^{1}H NMR (d_4 MeOH): 7.87 ppm (2 H, m, Ar); 7.51 (1 H, m, Ar); 7.48 (1 H, t, *J* = 7 Hz, (aminomethyl)benzoyl C(3)H); 7.40 (1 H, s, aminothiazole C(5)H); 7.20 (1 H, d, *J* = 8 Hz, indane C(6)H); 7.05 (1 H, d, *J* = 8 Hz, indane C(7)H); 6.73 (1 H, s, indane C(4)H); 5.78 (1 H, s, CHAr); 4.12 (2 H, s, CH_2NH_2); 2.79 (4 H, m, indane C(1)H_2 and C(3)H_2); 2.00 (2 H, m, indane C(2)H_2).

HPLC (Luna 2, gradient 1): rt = 3.21 minutes.

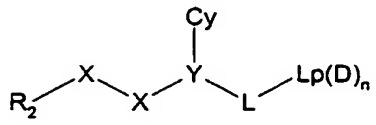
LC/MS (Luna 2, gradient 4): rt = 1.78 minutes; 422 $(MH)^+$.

The compounds exemplified hereinabove have been found to be

inhibitors of tryptase by the method of Tapparelli et al., (1993) J. Biol. Chem., 268, 4734 to 4741.

CLAIMS

1. A serine protease inhibitor compound of formula (I)



(I)

where R_2 represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, substituted in the 3 and/or 4 position by R_1, and optionally substituted in the position alpha to the X-X group by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_1 independently represents aminoalkyl;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group;

D is a hydrogen bond donor group;

n is 0, 1 or 2;

R_{1a} represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl; and

R_{1b} and R_{1c} are as defined for R_{1a};

or a physiologically tolerable salt thereof.

2. A compound as claimed in Claim 1, in which n is 0.

3. A compound as claimed in Claim 1 or Claim 2, in which X-X is selected from -CH=CH-, -CONH-, -CONR$_1$-, -NH-CO-, -NH-CH$_2$-, -CH$_2$-NH-, -CH$_2$O-, -OCH$_2$-, -COO-, -OC=O- and -CH$_2$CH$_2$-

4. A compound as claimed in Claim 3, in which X-X is CONH.

5. A compound as claimed in any one of Claims 1 to 4, in which Y is a CR_{1b} group and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X.

6. A compound as claimed in any one of Claims 1 to 5, in which Y is CH.

7. A compound as claimed in any one of Claims 1 to 6, in which Cy represents an optionally R_{3a} substituted cycloalkyl, piperidinyl, phenyl, thienyl, thiazolyl, pyridyl, or naphthyl group.

8. A compound as claimed in Claim 7, in which R_{3a} is selected from: hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, methoxymethyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, aminoacetyl, formylamino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphenyl, imidazol-4-yl, hydrazido, 2-methylimidazol-4-yl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy or trifluoromethyl.

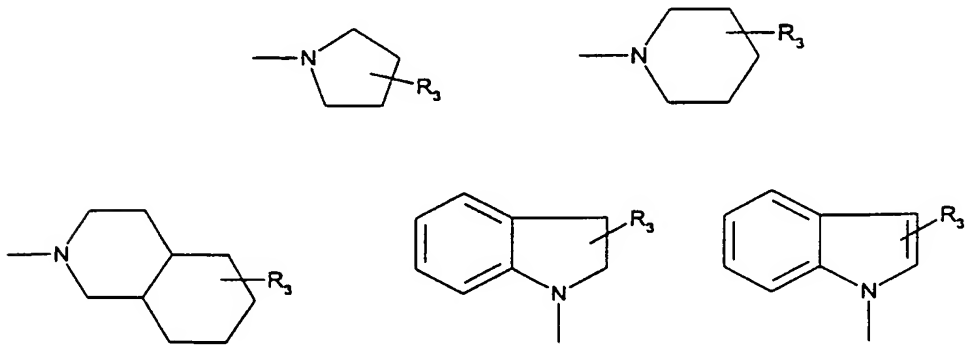
9. A compound as claimed in Claim 8, in which Cy is selected from cyclohexyl, piperidin-4-yl, phenyl, 4-aminophenyl, 4-hydroxphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 4-hydroxmethylphenyl, 3-hydroxymethylphenyl, 2-hydroxymethylphenyl, 4-phenylphenyl, 2-aminothiazol-4-yl, 2-formylaminothiazol-4-yl, 2-aminothiazol-5-yl, 2-formylaminothiazol-5-yl, 4-aminopyrid-3-yl, 3-amino-pyrid-4-yl and naphth-1-yl.

10. A compound as claimed in any one of Claims 1 to 9, in which L represents CO, CH_2NH, $CONR_{1d}(CH_2)_m$, $(CH_2)_mN(R_{1d})CO(CH_2)_m$, $(CH_2)_{m+2}$, $CO(CH_2)_m$, $(CH_2)_mCO$, $(CH_2)_mOC=O$, $(CH_2)_mO$, $CH=CH(CH_2)_m$, SO_2, SO_2NR_{1d}, $SO_2(CH_2)_m$, $(CH_2)_mSO_2$ or $(CH_2)_mSO_2NR_{1d}$ (where each m is independently 0 or 1 and R_{1d} is as defined for R_{1a}).

11. A compound as claimed in Claim 10, in which L is CO, CONH, CH_2NHCO or $CONHCH_2$.

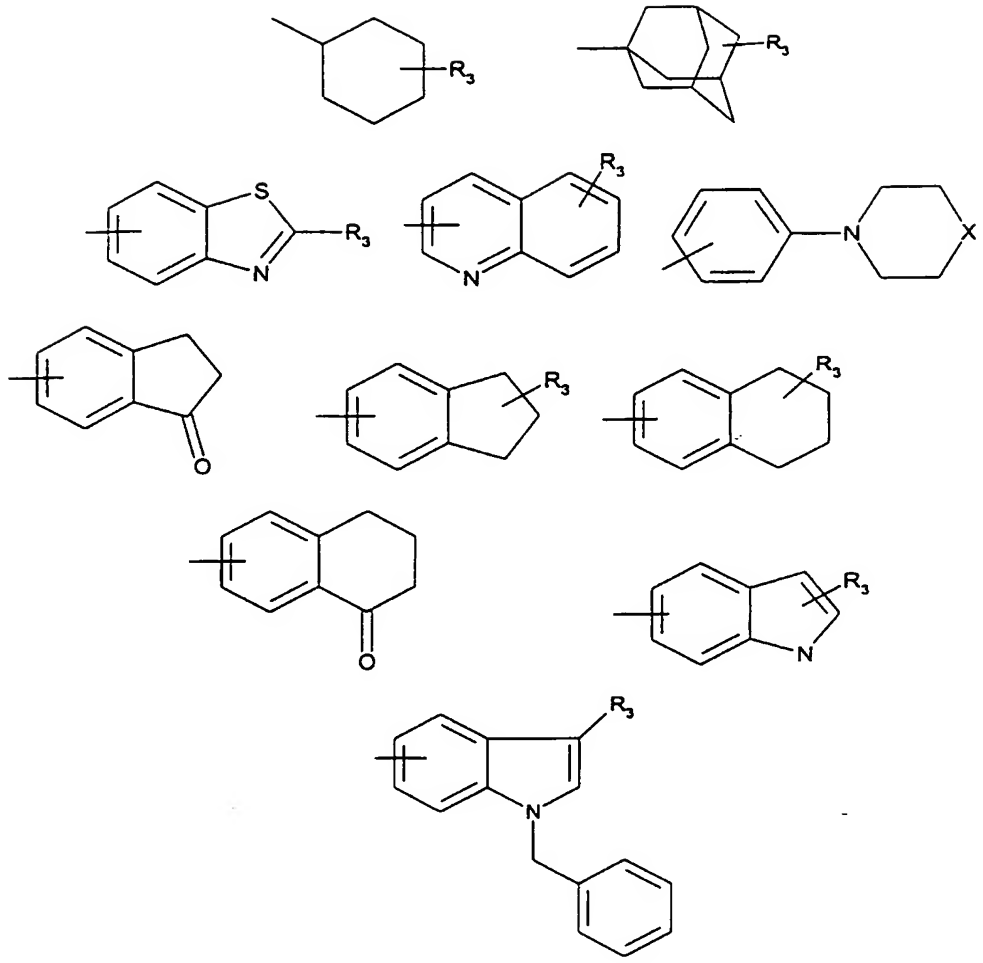
12. A compound as claimed in any one of Claims 1 to 11, in which Lp is an alkyl, alkenyl, carbocyclic or heterocyclic group, or a combination of two or more such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, NR_{1e}-CO-, NR_{1e} linkage (where R_{1e} is as defined for R_{1a}), optionally substituted by one or more oxo or R_3 groups in which R_3 is alkylaminocarbonyl, alkoxycarbonylamino, N-alkylaminoalkanoyl, N-alkanoylaminoalkanonyl, C-hydroxyaminoalkanoyl or is as defined for R_{3a}.

13. A compound as claimed in Claim 12, in which in which L represents CO and Lp represents



14. A compound as claimed in Claim 13, in which R_3 represents hydrogen, hydroxyl or alkylaminocarbonyl.

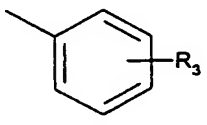
15. A compound as claimed in Claim 12, in which L represents CONH and Lp represents



in which X is CH or N.

16. A compound as claimed in Claim 15, in which R_3 is hydrogen, amino, hydroxy, alkyl or aminoalkyl.

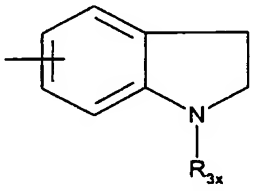
17. A compound as claimed in Claim 12, in which L represents CONH and Lp represents



in which R_3 is alkylaminocarbonyl, N-alkylaminoalkanoyl, N-alkanoylaminoalkanonyl, C-hydroxyaminoalkanoyl, hydrogen, alkoxy, alkyl, aminoalkyl, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl, alkylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl.

18. A compound as claimed in Claim 17, in which Lp is phenyl, 3-cyano-4-methylphenyl, 3-aminocarbonylphenyl, 4-aminocarbonyl-phenyl, 4-chloro-3-aminocarbonyl-phenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 3-aminomethylphenyl, 4-methyl-3-acetylaminophenyl, 4-(1-hydroxethyl)phenyl and 4-isopropylphenyl.

19. A compound as claimed in Claim 12, in which L represents CONH and Lp represents



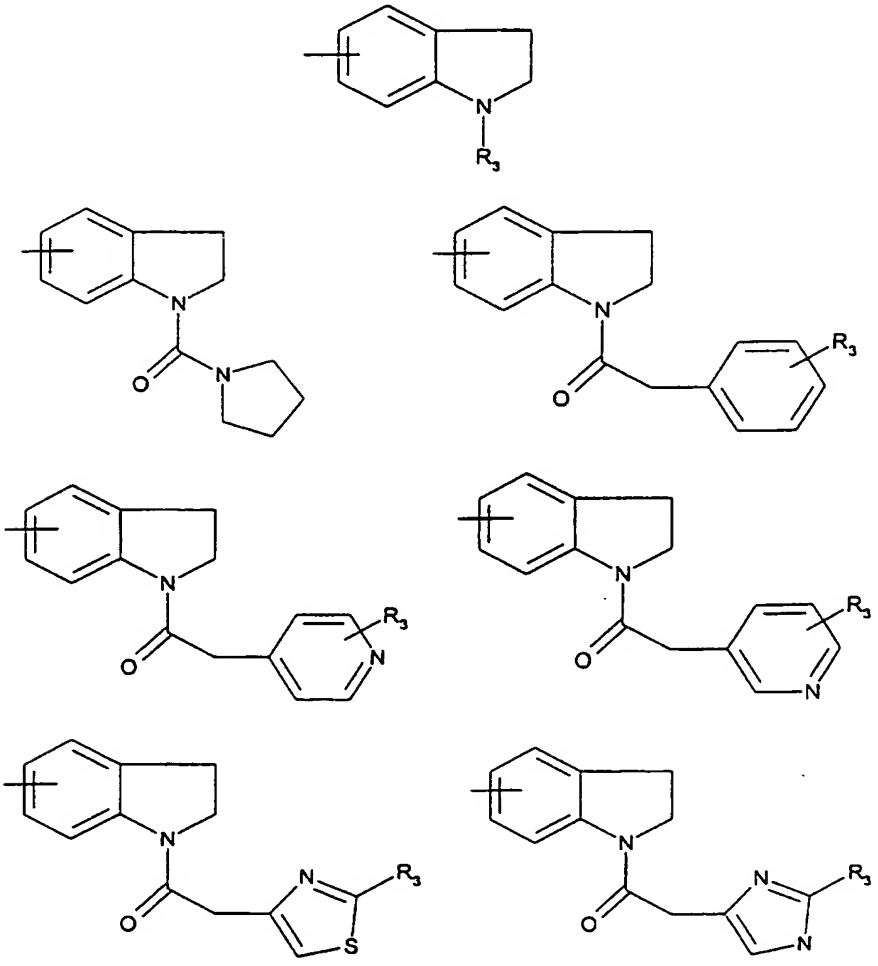
in which R_{3x} represents R_3 or a group of formula

$$-(CO)_p-(G_1)-R_j$$

in which p is 0 or 1; G_1 represents (1-3C)alkanediyl or, when p is 1, a bond; and R_j represents a carbocyclic or

heterocyclic group, optionally substituted by R_3.

20. A compound as claimed in Claim 19, in which Lp is selected from

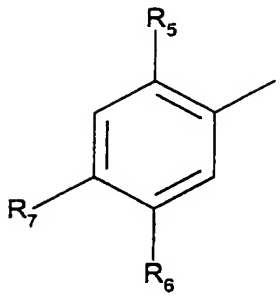


in which (i) when R_3 is a substituent on the 1-position of a 2,3-dihydroindolyl group, it represents alkylaminocarbonyl; N-alkylaminoalkanoyl; N-alkanoylaminoalkanonyl; C-hydroxyaminoalkanoyl; hydrogen; alkyl; alkanoyl; alkoxycarbonyl; acyloxymethoxycarbonyl; aminoalkyl;

aminoalkanoyl; hydroxyalkyl; hydroxyalkanoyl; alkoxyalkyl; or alkanoylamino; and (ii) when R_3 is a substituent on a phenyl, thiazolyl, imidazolyl or pyridyl group, it is hydrogen, amino, alkyl or aminoalkyl.

21. A compound as claimed in Claim 12, in which Lp is selected from: 1-(N-methylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-acetylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-acetylalaninoyl)-2,3-dihydroindol-6-yl; 1-(serinoyl)-2,3-dihydroindol-6-yl; 1-(threoninoyl)-2,3-dihydroindol-6-yl; 2,3-dihydroindol-5-yl; 1-methyl-2,3-dihydroindol-6-yl; 1-acetyl-2,3-dihydroindol-6-yl; 1-propanoyl-2,3-dihydroindol-6-yl; 1-(2-methylpropanoyl)-2,3-dihydroindol-6-yl; ; 1-(3-methylbutyryl)-2,3-dihydroindol-6-yl; 1-(2-hydroxpropanoyl)-2,3-dihydroindol-6-yl; 1-hydroxacetyl-2,3-dihydroindol-6-yl; 1-aminoacetyl-2,3-dihydroindol-6-yl and 1-alaninoyl-2,3-dihydroindol-6-yl; 2,3-dihydroindol-5-yl, 1-prolinoyl-2,3-dihydroindol-6-yl, 1-phenylacetyl-2,3-dihydroindol-6-yl, 1-(2-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(3-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-(3-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-imidazol-4-ylacetyl-2,3-dihydroindol-6-yl, 1-(2-aminothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl, and 1-(2-formamidothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl.

22. A compound as claimed in any one of Claims 1 to 21, in which R_2 is a group of formula



wherein R_5 is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R_6 and R_7 which may be the same or different represent hydrogen or R_1.

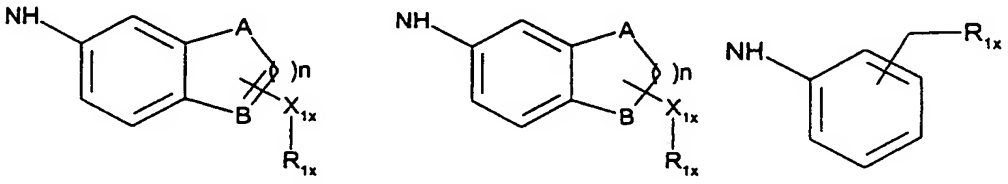
23. A compound as claimed in Claim 22, in which R_1 is a group of formula $-CH(R_{6a})NH_2$ in which R_{6a} is hydrogen or methyl.

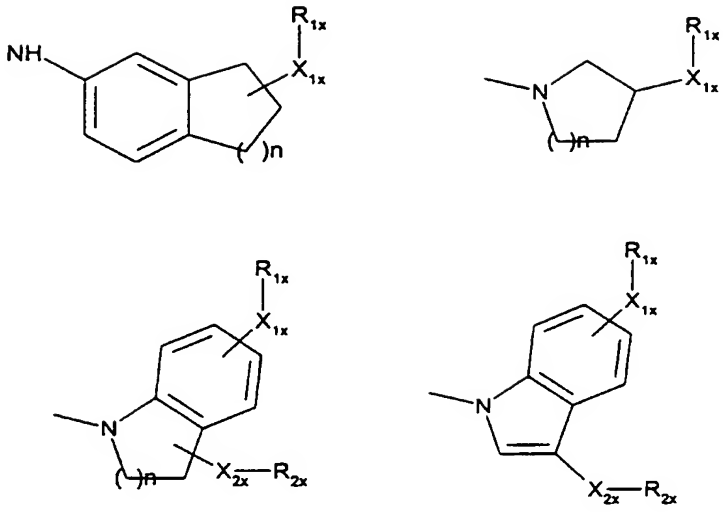
24. A compound as claimed in Claim 22 or Claim 23, in which R_5 is amino or hydrogen.

25. A compound as claimed in Claim 24, in which R_5 is hydrogen.

26. A compound as claimed in Claim 25, in which R_2 is 3-aminomethylphenyl.

27. A compound as claimed in any one of Claims 1 to 27, in which L-Lp(D)$_n$ is COLx- and Lx is





wherein:

A and B are independently chosen from NH, N, O, S, CH, CH_2;

X_{1x} and X_{2x} are independently chosen from $(CH_2)_m$, $(CH_2)_mCH=CH(CH_2)_p$, $CO(CH_2)_m$, $NH(CH_2)_m$, $NHCO(CH_2)_m$, $CONH(CH_2)_m$, $SO_2NH(CH_2)_m$, $NHSO_2(CH_2)_m$;

n is 1 or 2;

m is 0 to 2;

p is 0 to 2;

R_{1x} and R_{2x} are independently chosen from hydrogen, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, oxo, heterocyclo optionally substituted by R_{3x}, cycloalkyl optionally substituted by R_{3x} or aryl optionally substituted by R_{3x}; and

R_{3x} is hydrogen, alkoxy, alkyl, amino, hydroxy, alkoxy, alkoxycarbonyl, halo, cyano, nitro, thiol, sulphonyl, or sulphenyl.

28. A compound of formula I as claimed in Claim 1 and as named in any one of the Examples herein, or a physiologically tolerable salt thereof.

29. A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 27 together with at least one pharmaceutically acceptable carrier or excipient.